JOURNAL OF THE

American Geriatrics Society

Official Journal of the American Geriatrics Society

Volume IX *October, 1961* Number 10

LIMITATIONS OF THE SERUM CHOLESTEROL LEVEL AS A DIAGNOSTIC INDEX OF CARDIOVASCULAR STATUS

G. DOUGLAS TALBOTT, M.D.*

American Medical Research Foundation, Dayton 2, Ohio

Many physicians, as well as lay persons, put too much credence in the serum cholesterol level as an index of cardiovascular condition.

The word "cholesterol" has long been associated with atherosclerosis, and a high cholesterol level has come to be equated with coronary heart disease. One of two equally dangerous attitudes may be the result of conclusions drawn on the basis of an isolated reading: 1) if the cholesterol concentration is within the accepted range, the patient may acquire a false sense of security and frustrate all medical precautions; or 2) if the concentration is high, the patient may succumb to unnecessary fear, burden his life with needless worrisome restrictions, and become a "cholesterol cripple." Stimulated by the plethora of cholesterol-oriented material that is presented almost daily through the mass media, patients who represent one attitude or the other are becoming an increasing medical problem.

The physician is obligated to discourage both of these attitudes. Evidence now indicates that cholesterol, of itself, has much less to do with coronary atherosclerosis than was formerly supposed; it is not even an accurate reflector of other lipid elements which may prove to be more closely correlated with coronary atherogenesis. Proof already exists that the solitary cholesterol determination is wholly unreliable as a criterion of cardiovascular health, and can even be dangerously misleading.

CHOLESTEROL, LIPIDS AND ATHEROSCLEROSIS

Let us briefly review the steps by which cholesterol became accepted as an index of coronary atherosclerosis.

Many investigators believe that the first recognizable morphologic sign of atherosclerosis is the deposition of lipids in the intima of the artery (1–8). These deposits, supplemented by such elements as fibrin, protein, calcium and apatite create plaques which progressively obstruct the normal flow of blood. There is evidence that the aorta is the first site of such deposits (9, 10), but the order in

* Medical Director, American Medical Research Foundation, 1230 Fidelity Medical Building, Dayton 2, Ohio.

which other sites become involved, the rate of progression, and whether or not the condition will eventuate in a fatal complication, are events which depend upon a maze of contributing factors, of undetermined relative importance. Age, race, sex, body-build, diet, personality, exercise, occupation, stress, the use of tobacco, alcohol and salt, and even economic status, are some of the many etiologic agents which have been considered. Among this aggregation of variables, the deposition of lipids continues to be the one demonstrable constant.

Cholesterol is the lipid historically regarded as the logical target for the attack on atherosclerosis. Though it is only one element in a wide lipid spectrum, it was marked for incrimination as soon as Vogel identified the substance in atheromatous aortas during the mid-nineteenth century. It received no further attention until Aschoff, studying a series of aortas more than fifty years later, reported that a high concentration of cholesterol was invariably present in atheromatous vessels. Soon keen interest was aroused by Ignatowski's demonstration that atherosclerosis could be rapidly developed in rabbits if they were fed an unnatural diet high in cholesterol. But the climax came about 1913, when Anitschkow showed that atheromatous lesions could be produced in the rabbit at will, simply by adding pure cholesterol to the normal food (11).

For many investigators, that event incontrovertibly condemned cholesterol as the primary cause of atherosclerosis and all its complications, including coronary occlusion. In their opinion, future control of the disease hinged entirely upon recognition and correction of an elevated serum cholesterol level. This concept posed two needs: a practical means of measurement, and an effective method of control. The first was soon satisfied. Within four years after Aschoff published his momentous report, Windaus devised a quantitative test for serum cholesterol; improvements and simplifications followed rapidly, keeping pace with an increasing interest in lipids. Unfortunately, the second need was not so easily met. It became apparent that various tissues were able to manufacture cholesterol endogenously, contributing toward maintenance of a given level in the serum regardless of cholesterol variations in the diet (12). The problem of controlling atherosclerosis was not yet solved.

Although Virchow had remarked on the fatty nature of atheroma as early as the middle of the nineteenth century, it was not until about 1928 that lipid fractions other than cholesterol were recognized in atheromatous plaques. At that time, Schoenheimer demonstrated the presence of both phospholipid and cerebroside in atheromatous aortas. But the isolation and measurement of these fractions required laboratory procedures much more difficult and time-consuming than did the test for cholesterol, and hence the study of these lipids was neglected (13). Other lipids subsequently identified have proved at least equally tedious to measure. Therefore, cholesterol has been accepted as the most practical index of the serum lipid level, and the most reliable indicator of an impending coronary occlusion.

The possibility of a site differential in the deposition of lipid fractions has further contributed to overestimation of the importance of cholesterol. In the past, the majority of histologic studies were concerned with the aorta alone, since that

is the vascular tissue which most readily lends itself to microscopic study in smaller laboratory animals. Increasing refinements in techniques recently made possible some comparative studies of atherosclerosis at other sites, and thereby revealed interesting variations in lipid deposition. Segmental differences reported by Hojman *et al.* (9) in 1959, and other independent discoveries made at about the same time, have increasingly indicated the importance of these variations. For example, when Böttcher *et al.* (14) analyzed lipids isolated from both the aorta and the coronary arteries of atherosclerotic subjects they found that whereas the aorta showed the anticipated high concentration of cholesterol, the coronaries showed a predominance of triglyceride. Albrink and Man (15) reported that when the three major lipids were evaluated, the most clearcut separation between normal and diseased coronary arteries in human subjects was on the basis of an elevated concentration of serum triglycerides. These and other investigators are now exploring the possibility that a high level of triglycerides or of some other lipid fraction may be a better indicator of coronary atherosclerosis than is a high level of cholesterol.

INCONSISTENCIES IN THE CHOLESTEROL-CORONARY RELATIONSHIP

A critical survey of the literature reveals innumerable discrepancies in the assumed cholesterol-coronary relationship and points to the danger of depending upon an elevated cholesterol level as either pathognomonic of coronary atherosclerosis or predictive of coronary occlusion.

Since it seems established that the incidence of cornary disease is several times greater among men than among women under 40 years of age (2, 16–19), one would expect the cholesterol level to be correspondingly higher among the male sex. There is no evidence of this. On the contrary, at least one study emphasizes the similarity of the cholesterol level in both sexes for this age group (20).

We have noted in the literature that although a persistent cholesterol level above 250 mg. per 100 ml. does not necessarily signify an impending coronary attack (21), neither does a level below 200 mg. per 100 ml. carry any assurance of safety (22–24). Barnes (25) studied cholesterol in more than 400 adults seen repeatedly over a period of years and found that in persons with the highest initial levels, clinical coronary disease did not develop during the time of observation. On the other hand, Brunner and Lobl (26) reviewed a group of 74 coronary patients under the age of 62 years, and found that nearly half of them had a serum cholesterol level within the upper limit of 250 mg. per 100 ml., at least one being as low as 145 mg. per 100 ml. Schlessinger *et al.* (27) noted that total serum cholesterol concentration was an unsatisfactory discriminator between normal and coronary groups. Obviously, the so-called "normal" serum cholesterol range of 200–250 mg. per 100 ml. has no dependable relationship to coronary atherosclerosis in individual cases.

PITFALLS IN DEPENDENCE UPON SOLITARY CHOLESTEROL DETERMINATIONS

Surveys indicate that the serum cholesterol level differs considerably from time to time in the same person, without definite relationship to either state of health

or advancing age (28, 29). This has been observed among both confirmed coronary patients and persons without known cardiovascular lesions. Steiner and Domanski (30) surveyed the literature and reported a study of 15 coronary patients and 10 controls, in all of whom many successive cholesterol determinations were made over periods varying from three to twenty-six months. The individual average level was computed for the time under observation, and standard deviations were calculated for each person. In the coronary group the variations ranged from 19.5 to 36.2 per cent; in the control group the range was from 3.2 to 10.3 per cent. Man and Peters (31), studying a group of people in whom they remeasured the serum cholesterol levels after intervals of ten to twenty years, found variations in individual cholesterol concentrations, but no consistency in the direction of change which could be correlated with advancing years. Watkin and associates (32) made a study of cholesterol variability in adult men, and also concluded that variations could not be directly related to the age of the subject. Perkins and co-workers (33) found a variation of approximately 25 per cent in the individual records of a series of five weekly cholesterol determinations in 22 healthy young men. Such examples, culled from the literature, illustrate the fallacy of relying on a single cholesterol determination for any purpose whatsoever.

Even the reliability of the laboratory value for an isolated cholesterol determination is open to serious question. Recently an account was published of a single blood sample which had been divided among five reputable laboratories for measurement of cholesterol (34). No two results agreed. More astonishingly, the five reports ranged from 180 to 312 mg. per 100 ml. Consider the span of diagnostic error encompassed by such variation, and the potential danger of basing any conclusion as to cardiovascular status on a single cholesterol determination!

DIFFICULTIES OF ESTABLISHING NORMAL VALUES

Even if the laboratory report is accurate beyond dispute, there is no universal normal standard with which it can be compared. The Bantu of South Africa constitute the classic example of a people with a low serum cholesterol level, the mean being about 147 mg. per 100 ml. (35). Agricultural workers of Guatemala have an even lower mean level—about 140 mg. per 100 ml. (36). American men in good health have an average level ranging from 200 to 250 mg. per 100 ml. Values in people of western Europe fall between these two extremes. Bronte-Stewart *et al.* (37) surveyed three racial groups on Cape Peninsula and found a significant difference in the incidence of coronary disease between groups having essentially the same serum cholesterol level. In their series of cases, the closest correlation was found between economic status and cholesterol level. Keating's (38) survey of the world literature in 1957 disclosed "normal" values ranging from 78 through 492 mg. per 100 ml., a tremendous spread that could by no means be all accounted for on a racial basis. Obviously, no universally normal serum cholesterol value exists.

It is not even possible to establish a normal value for such a limited group as the adult American male. In testing 612 normal medical students, Thomas and Eisenberg (39) found some serum cholesterol levels as high as 407 mg. per 100 ml.

and others as low as 108 mg. per 100 ml. Lawry and associates (40), after examining the cholesterol values in 1,968 healthy Americans, concluded that an outstanding characteristic of the serum cholesterol level among adults of the same sex, race, age and clinical status, is its great variability.

INADEQUACY OF THE SERUM CHOLESTEROL LEVEL AS A LIPID INDEX

Even though not in itself a reliable index of coronary atherosclerosis, the serum cholesterol level might still serve a useful diagnostic purpose if it faithfully reflected the action of the entire lipid spectrum. But this it does not do.

The first unmistakable evidence that the cholesterol value indicates neither the quantity nor the behavior of some of the other lipid fractions was reported by Keating in 1957, after study of the lipid patterns in 50 adult males. In that project, the cholesterol, phospholipid, and beta-lipoprotein levels for each subject were compared with average values as determined from representative reports in the literature. When both the absolute values and the percentile deviations were plotted on graph scales, cholesterol deviations could not be consistently correlated with those of either of the other lipid elements. This led to the hypothesis that the level of cholesterol is not a reliable indicator of the patterns of other lipid fractions.

Support for this hypothesis came from a later experiment made in our laboratory, primarily to determine the effects of salt-loading on induced hyperlipemia (41). Nine blood factors were measured—first with the subject fasting, and then at zero, two, four and twenty-four hours after infusion of fat. The results were compared with similar measurements made after one week of a sodium chloride regimen. The finding of greatest statistical significance was the consistently wide divergence between cholesterol and triglyceride levels in response to salt loading.

Such differences in behavior between cholesterol and other lipid fractions may explain many of the discrepancies in the cholesterol-coronary relationship. Some other lipid fraction, possibly triglycerides, may prove to be a better index of coronary atherogenesis than is cholesterol. Adequate exploration of this possibility will require much more time.

Meanwhile, the cholesterol determination probably will continue to be a part of every careful cardiovascular examination for some time to come, partly in response to public demand, and partly because few laboratories are yet prepared to measure other lipids. However, the diagnostician should never rely upon a single determination. In the absence of clinical symptoms and unsupported by an upward trend in the levels of other lipids, an elevation in the concentration of serum cholesterol should not be made the basis of undue concern. A multidimensional approach to evaluation of the cardiovascular status should supplant the present emphasis on the serum cholesterol level.

SUMMARY

As the first recognized and most easily measured lipid fraction of the serum, cholesterol has assumed an undeserved place of importance in the evaluation of atherosclerosis and the prognosis of coronary heart disease.

The wide variations in serum cholesterol levels in both health and disease, in the same subject as well as between subjects, make it virtually impossible to establish a "normal" serum cholesterol level as a standard for comparison, and nullifies the value of a single determination.

Increasing refinements of biochemical techniques have recently enabled investigators to measure other lipid fractions, such as the triglycerides, and to observe that cholesterol does not reflect these other fractions in either quantity or behavior.

In the light of present knowledge we are not justified in emphasizing a single cholesterol determination. Accepting such a laboratory result as a basis for the diagnosis of advanced atherosclerosis or for the prognosis of an impending coronary occlusion is unwarranted. Nor is there any justification for assuming that a so-called "normal" serum cholesterol level indicates freedom from atherosclerotic disease.

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RELATIONSHIP OF THE MEDICAL PROFESSION TO GOVERNMENT SUPPORTED ALCOHOLISM PROGRAMS

MARVIN A. BLOCK, M.D.*

Buffalo, N. Y.

Reversal of the title of this article to "The Relationship of Government Supported Alcoholism Programs to the Medical Profession" would make no difference. It is much more important to recognize the definite and intimate relationship between these programs and the medical profession. It is one which should be of the utmost interest, not only to the people engaged in the programs and to physicians generally, but to all other professions, as well. This statement is almost redundant, because members of the medical profession obviously are an integral part of such programs. As an organization, however, the profession rarely participates officially, even though it is aware of the important part which it must play in the work of the programs.

PROGRAM OF THE COMMITTEE ON ALCOHOLISM OF THE AMERICAN MEDICAL ASSOCIATION

At its very inception, the Committee on Alcoholism of the American Medical Association drew up an 18-point program which was published in the Journal of the American Medical Association. The seventh point of that program reads, "To stimulate in each state health department or division on alcoholism plans for activity on the public health aspects of the problem, including medical prevention and early detection, and to encourage study of the epidemiology, diagnosis, and treatment of the disease from a public health point of view." With this statement, organized medicine committed itself to aid in every possible way the study and treatment of alcoholism. Since there is direct reference to state health departments, this necessarily means government supported programs. The Committee's 18-point program was primarily drawn for distribution to State medical societies in an effort to interest these organizations in becoming active in the field of alcoholism at their state's levels. The American Medical Association's Committee does this at the national level. It is for this reason that Point 7 specifically mentions state health departments. The same program is offered to county medical societies with the suggestion that the county medical society carry on this activity with county health departments at that level. Hence, we find medical organizations at the national, state, and county levels urged to cooperate with the health departments at their respective levels.

Point 2 of the program, among other things, states, "To inform physicians of symptoms, diagnosis, and therapy, and inform and advise through the organized

* Chairman, Committee on Alcoholism of the Council on Mental Health of the American Medical Association.

Address: 371 Linwood Avenue, Buffalo 9, N. Y.

medical societies, other allied professions." Again there is a pledge by the medical profession to aid any program which helps alcoholics.

The sixth point of the program states, "To establish minimal standards of treatment for alcoholics, and to encourage study of the illness and its treatment by a) education in medical schools and hospitals, through county medical society programs, and b) rehabilitation—the coordination of present treatment programs, and promotion of demonstration centers." Since many of the treatment programs and demonstration centers are operated by the government, here again, the profession offers to cooperate with such government supported alcoholism programs.

Besides cooperation with state alcoholism programs, Point 11 of the Committee's program states, "To develop adequate statistics on alcoholism for each state." Again, this would necessitate a direct relationship with government operated programs in order to ascertain such statistics. "The Committee should study and make known to society members, sources for advisory and educational services on the subject." This is Point 12 of our program, and necessarily includes government supported operations on alcoholism as one of the resources suggested to its members. As a matter of fact, practically all of the 18 points of the Program of the Alcoholism Committee of the American Medical Association apply to relationship with government supported alcoholism functions.

RELATIONSHIP TO ORGANIZED MEDICINE

The medical organization

Knowledge of a subject is not enough to guarantee success. Most of us recognize the tremendous importance of the personalities of individuals working in any field. In the field of alcoholism, this is as important as knowledge. The ability to associate with people, communicate with them, and impart to them the enthusiasm and information which one must have about a field before he can succeed in it, is the requirement for a good staff member. The training of staff is essential, and time spent in the discussion of public relations could prove of great value. Just as there is no general treatment for alcoholics, there is no general rule for such public relations. Specific localities call for individual approaches, much as the alcoholic patient requires treatment tailored for him as an individual. One can apply routine only to a limited extent. The ability to evaluate one's locality and prescribe the approach which will bring about the greatest interest of professional groups in that area, is a responsibility of a competent staff member. It can be as important to concentrate on this part of the facility's activity as on any other phase. Without the support of co-existing professional groups and the public at large in a given area, we cannot hope to achieve the success which our work and objectives warrant.

The organized medical profession as such cannot very well participate in the operation of any program outside of its own constituent organizations. It is always available, however, for suggestions, consultations, and advice in which it is qualified. Because of its authoritative nature, the organized medical profession tries not to presume, and prefers in most cases to have its advice sought rather

than to offer it gratuitously. It is not always invited to participate officially. There are many occasions when programs involving spheres of medical practice are carried out by individuals and by organized groups who do not consult the official organized medical profession. Individual physicians, competent to be sure, are often invited to join in these programs, either actively or as consultants, but the official medical organization may be omitted. How, then, can it participate? Would it not be advantageous for these programs to invite the medical profession to participate officially? Certainly the interest of the profession cannot be questioned. As a matter of fact, the fifth point of the American Medical Association's program for 1961, which the President of the American Medical Association (Dr. Vincent Askey) projected when he was inaugurated, stresses mental health. This includes the problem of alcoholism. The year 1961 will see a tremendous effort by the entire American Medical Association to increase interest in mental health generally and alcoholism in particular. This program, with emphasis on alcoholism, is in the process of organization.

Numerous professional areas are represented. By and large, most of us come from urban communities where there are programs on alcoholism. These include information centers, counselling centers, clinics, and rehabilitation programs. The desirability of a relationship between these various government supported agencies and the medical profession as an organization, in the areas in which these facilities operate, is obvious.

A few doctors in each community are more particularly interested in the problem of alcoholism than others of their profession. Usually, these few doctors are invited to participate in the program of the government sponsored facilities, and doubtless they make a contribution in their respective localities. They serve on advisory boards, are employed in the clinics on a full-time or part-time basis, and often act as consultants to these various facilities. In the minds of the community, they become associated with the problem of alcoholism. As a result, private patients seeking help for the disease are referred to these physicians by the various local facilities. There is no doubt that these physicians are deserving of this consideration, but it is also obvious that this practice limits the number of physicians who treat alcoholics in a given area. We all concede that it is necessary that more physicians be interested in the management of alcoholic patients in their practices. How, then, can this be accomplished if all the interest is concentrated in a few physicians. It is here that the medical profession as an organization can be of great value to the state supported agency in a given area.

Agencies are frequently called by individuals who want attention but who have no desire to go to clinics. When inquiries are made for sick alcoholics requiring medical help, the names of interested physicians related to the facility are usually given the inquirer. Here a suggestion can be offered which has succeeded universally in areas where it has been adopted. Instead of giving the name of a physician to the inquirer, the questioner should be directed to call his local medical organization, usually his county medical society, and ask the society for the names of physicians treating alcoholics. It now becomes the society's responsibility to provide physicians for those making the inquiry. This involves the medical society

in the care of the alcoholic patient who wants a physician and who does not wish to attend a public clinic. The medical organization itself now becomes responsible to some degree for the handling of the problem of alcoholism in its community. Eventually, it will provide a list of physicians. As the demand grows, the list will become longer, and the society will become more and more interested. A few inquiries of this type to the medical society will produce results, since no medical organization wishes to be lacking in its service to the public.

The individual physician and his training

It is generally agreed in the medical profession that the treatment of an illness belongs in the hands of medical men. By and large, everyone concurs in this. However, in some state supported clinics the administrators are non-medical people. This may give rise to resentment on the part of some physicians. It is a sensitive area which must be taken into consideration. Without discussing the relative merits of medical versus non-medical administration in a health facility, it might be wise for people without medical training to consider this when working with the medical profession. The wise non-medical staff personnel learns how to work with physicians without causing resentment. Sometimes they find it advantageous to assign a physician of their staff to deal with the medical profession when necessary. This may not be a serious factor in the administration of government supported facilities, but it has been known to deter some physicians from participating in the activity of health clinics.

In far too many instances, general physicians do not understand the problem of alcoholism in its medical, psychiatric or sociologic aspects. One cannot expect a physician to take training in treating a specific disease if he is not going to be called upon to use such training. Given the opportunity to care for alcoholic patients, however, any physician in general practice will make it a point to learn more about that illness, both in the acute and post-acute phases. As in every other area, it is a question of the supply meeting the demand, when the demand is there. It has been said that physicians often refuse to treat alcoholic patients. This attitude is rapidly changing. The response to the educational programs on alcoholism has been tremendous, and more and more physicians are now treating these patients. Inquiries at American Medical Association headquarters regarding the subject of alcoholism are increasing progressively, and demands for literature increase each year.

Many physicians unacquainted with the problem of alcoholism are completely at a loss how to proceed with these patients. This presents a most frustrating problem. Often it is easier for such physicians to refuse to see such patients than to face the cold reality of ignorance about how to treat them properly. If opportunities were afforded physicians to learn about the care of these patients without losing time from their practices, they would respond favorably. If they could refer such patients to a facility for evaluation and a complete report, to be returned to them along with recommendations for treatment, they would feel more adequate and their interest would be greater. A valuable service could be made available to the practicing physicians of a community if a state supported clinic in that area

could provide such consultation service. It would make for greater cooperation between the practicing physicians and the clinic. Such a facility also could include in its activities educational opportunities for physicians in its area. This education could be offered to the organized profession in the locality where the program exists. As the calls to the medical society increase, and the number of physicians to whom these patients are referred grows, there will be a greater demand for such education on alcoholism. If this training could be made available by the public facility, the cooperation between the medical organization and the facility could be cemented, and the efficiency of both increased.

HOSPITALIZATION OF ALCOHOLIC PATIENTS

Hospitalization of patients in the acute stage of alcoholism is one of the vexing problems with which we are confronted. Misunderstanding of the alcoholic and his difficulties has led to resistance on the part of hospitals to the admission of such patients. Even government sponsored programs find it hard to obtain hospital care for alcoholic patients, and cannot understand why the medical profession does not take a greater part in this matter. This, again, becomes a question of education. Point 5 of the A. M. A. Committee program states, "To educate hospital authorities in each state to open their hospitals for the in-patient treatment of the alcoholic, especially in the acute stage, and to encourage the establishment of out-patient services for alcoholics in general hospitals where feasible for follow-up treatment." Many out-patient clinics in general hospitals are government supported. The staffs of such programs should interest hospital administrators and the heads of various departments in the treatment of alcoholism. A seminar sponsored by these facilities can often help to change the attitude toward patients. When board members of hospitals are resistant to the admission of alcoholics to their institutions, special programs for such board members can also be of great value.

In 1956, the American Medical Association adopted a resolution on the hospitalization of alcoholic patients. Despite the fact that the American Medical Association and the American Hospital Association have passed such resolutions asking general hospitals to admit alcoholics, many hospitals have not yet accepted this program. Only recently, the Commission on Accreditation of Hospitals has taken up this matter, and we are looking forward to a change in these attitudes. However, we need the cooperation of the government sponsored programs to bring this about.

TRAINING OF INTERNS, RESIDENTS AND MEDICAL STUDENTS

The training of interns and residents must be encouraged, so that the men going into practice will know something about alcoholism. As of now, most of these young men are unable to get such training because of the absence of alcoholic patients in the training hospitals. The state sponsored programs should cooperate with local medical societies in action on this point. They can offer their staffs for teaching in the hospitals, so that resident physicians can learn the proper care of alcoholic patients. They can also offer their facilities as out-patient

departments for the training of interns and residents. This would not only add to the facility's efficiency by increasing its staff at little or no cost, but would also give the young doctors an opportunity to treat alcoholic patients on an outpatient basis, in the government sponsored clinics. When these physicians go into practice, they would then add to the roster which the facilities could call upon for assistance.

The American Medical Association with its Committee has completed a four-year medical school curriculum for teaching the management of alcoholism. This curriculum has been accepted by the Council on Education and Hospitals of the American Medical Association, and by the Association of American Medical Colleges. All of the medical schools on our continent have received this curriculum for the training of their medical students. A copy is available to anyone who requests it. Several years from now, we can expect that graduates of medical schools will have a greater knowledge of alcoholism than they have today.

OTHER PROFESSIONS

It is not enough, however, to limit this education to medical schools in a university. The management of alcoholism should also be taught in schools of social work, sociology, business administration, law, dentistry, nursing schools, graduate education, and other university schools. The medical profession can be called upon to aid in such education. Here, again, a government sponsored program can make its staff available to the faculties of these schools, to provide information necessary for the various areas of interest.

In every locality where a government sponsored program operates, we find organizations of physicians, psychologists, psychiatrists, social workers, nurses, educators, and information center personnel, as well as other professional organizations interested in advanced training for their members. Alcoholism is not necessarily a popular subject with many of these professional people. It may not occur to them to call upon government sponsored programs for help. It would be advantageous however, if such facilities were to suggest to these organizations a teaching program on alcoholism which could be offered to the members of these various professional organizations. An invitation to the program chairmen of such groups to visit the facility and see what is being done in the field of alcoholism, is an excellent way to introduce this subject. Professional people, once they learn something about this problem, are fascinated by the possibilities of aid to such patients. It is but a matter of offering an opportunity to them to learn something about it.

Many clergymen are used as consultants in alcoholism programs throughout the country. Their value in such a program can be enhanced if they can learn more about it from the medical point of view. Here is where the medical profession can be called upon to cooperate with the government facility in providing such special information. Unfortunately, many clergymen, along with others, believe that alcoholism involves primarily a moral breakdown. I remember speaking at a meeting in Massachusetts, and afterward discussing with several clergymen the matter of pastoral counselling for sick people. I asked them whether they at-

tended meetings on peptic ulcer, hypertension, and coronary heart disease, or other illnesses of this type. When they expressed surprise at the question, I suggested that they felt there was an element of a breakdown of morality in the alcoholic, and this was why they were particularly interested in the subject. They agreed that intellectually they did not believe that morality entered into it, but confronted with the idea that the same etiologic factors in alcoholism might also be present in the diseases mentioned, they immediately agreed that their fields could be widened. Clergymen are of tremendous value in the treatment of alcoholism when they are properly trained, but they must have some knowledge of the disease from the medical viewpoint before they can look upon it objectively. Without such training, they may be handicapped. The clergy could find no better place for education in the field of alcoholism than through the programs operated by the government, with the aid of the medical profession.

PUBLIC HEALTH PROGRAMS

The American Public Health Association has become extremely interested in alcoholism, and my last contact with them led me to believe that they were considering appointing a permanent committee for this problem. Here is an organization which cuts across all professional disciplines and can be of exceptional aid in promoting programs on alcoholism in all localities. Cooperation with this organization by government programs would enhance immeasurably the opportunities for reaching those suffering from this illness. A close liaison with the branches of the American Public Health Association which exist in practically all urban areas can be of mutual benefit to both that organization and the government program. As a matter of fact, many such programs are under the direct aegis of public health departments.

The National Council on Alcoholism with its more than 60 affiliates has a broad educational program which reaches all parts of the country. Government sponsored programs can cooperate with the affiliates of this organization in order to bring about maximal effort in combating the disease. Their combined efforts can fill many potential gaps in programs on alcoholism. Cooperation can benefit both programs and render the public a greater service.

Alcoholism represents but one of many public health programs. It is one which has not been popularly accepted. The public too often looks upon alcoholism as a self-induced disease, and its attitude is not a kindly one. It is the responsibility of those in the work to convince and interest others. It is too much to expect that the public will come to us for help in understanding alcoholism; we must go to them. The circumscribed areas in which most government programs, and perhaps also the medical profession, have operated in the past may be responsible to some extent for the lack of interest on the part of other organizations and the public. In practically every state, the medical society now has a committee on alcoholism or a committee which is devoted to the problem. In addition, we encourage these state committees to urge every county medical society to name such a committee. The state sponsored programs can be of help if they will call upon the various local medical societies of the counties in which

they operate, and ask for such a committee on alcoholism if one does not already exist. Such a request will meet with the approval of the county society, if not immediately, at least within a short time. If appropriate, a physician member of the staff could make the request of his own county medical society.

PUBLIC RELATIONS

There is no doubt that people working in government sponsored facilities for the care of alcoholics are competent in the treatment of alcoholism. It is not enough, however, to be competent in the field if one expects to get the cooperation of various professional groups in the area in which such a facility operates. The public relations part of these programs have often been neglected because of the interest in treating the individual patients. Yet these programs should be directed to the public as well as to the patient. Every effort should be made to interest and include members of the various professions.

Long association with a government sponsored program affords ample opportunity for observing where improvements can be helpful. The necessity for relating such programs to the medical profession cannot be overemphasized. It becomes a matter of initiative. This should be stressed by both the program staffs and the organized medical profession, in order to provide a greater service to the community.

RECENT STUDIES IN THE IMMUNOLOGY OF CANCER. VI. DETECTION OF CELL-BOUND AUTO-ANTIBODIES AND AUTO-ANTIGENS IN CANCER*

JACK G. MAKARI, M.D., DIPL.T.M.&H., SC.M.,†

with the technical assistance of

MARY FRANCES OPP, M.S.

Research Department, Muhlenberg Hospital, Plainfield, New Jersey

Auto-antibodies and auto-antigens are becoming progressively recognized as causative agents of diseases in man. The list of diseases attributed to an auto-immune mechanism is continuously increasing. Thus, in certain hemolytic anemias (1, 2), thyroiditis (3, 4), nephritis (5), adrenalitis (6), encephalomyelitis (7) and myelitis (8), such a mechanism is strongly implicated.

The evidence for these claims has been obtained from either the experimental production of such lesions in some cases, or the finding of bivalent antibodies (which precipitate or fix complement) in the sera of subjects with such diseases. The findings with the former approach are fairly convincing but they are hard to produce and are only possible in animals, not man. With the latter approach—total emphasis on circulating bivalent antibodies—only a minority of cases may thus be detected. Apparently immunologists have completely ignored univalent and fixed antibodies, both of which seem to play such a vital role in auto-immunity. In fact an "iron curtain" has been erected between immunology and allergy; between the antibodies which circulate in the blood and those which are fixed to certain tissues; between the antibodies which precipitate and the antibodies which immunize, as opposed to those which do not precipitate and those which do not immunize but instead sensitize.

More recently, in the search for fixed antibodies in certain diseased tissues, immunologists have resorted to indirect methods aimed at proving the presence of bound gamma globulins by the use of either the antiglobulin Coombs test (9) or immunofluorescent techniques (10, 11). But how specific are these methods?

Evidence of non-immune adsorption of serum proteins to red cells is accumulating and has been recently reviewed (12). Weakly positive reactions to the direct Coombs tests develop in non-immune hemolytic diseases such as sickle-cell anemia. Injury of the red cells by agents such as viruses can cause adsorption of albumin by the cells with a resultant positive reaction with the direct Coombs test if the test serum contains any anti-albumin (13). A positive result with the direct anti-globulin test seems to reflect in some instances the secondary fixation

* Parts I–V of this study were published in the August 1959 and January, August and September 1960 issues of this Journal.

† Director of Research, Muhlenberg Hospital.

of serum proteins, gamma globulin or non-gamma globulin, on or to a damaged membrane (14).

Furthermore, does the adsorption of gamma globulin on certain cells or its presence around the site of tissue injury mean that it is an antibody globulin? Can we selectively tag (with a fluorescent dye or a radioactive isotope) antibody globulins as distinguished from normal globulins?

Techniques are needed which can demonstrate the presence of cell-bound univalent antibodies and cell-bound antigens, and can detect the presence *in vivo* of auto-antibodies (*i.e.*, antibodies directed against the subject's own tissues) and auto-antigens. Elsewhere (15–17), the author has described such a method in which complexes formed by the subject's own antibodies and a polysaccharide antigen are used as the testing material, and the skin of the subject to be tested is selected as the site for the antigen-antibody reaction. It was on the basis of this approach that we first postulated the concept that cancer is an auto-hypersensitivity type of disease in which the subject becomes hypersensitive to his own antibodies when these are allowed to form complexes with polysaccharide tumor antigens.

An immunologic procedure is also needed for analyzing *in vitro* a piece of tissue from a human subject in terms of auto-antibodies (whether bivalent or univalent) and auto-antigens (whether complete or incomplete). In this report such a method will be described.

In our earlier work (18, 19), we successfully utilized the highly sensitive Schultz-Dale test for the detection of antigens in the serum of patients with cancer. We also found specific antigens in cancer tissue homogenates by this method. Burrows (20) has confirmed our work in man. Hauss (21) also has recently offered further confirmation of our approach. Baruah (22, 23) successfully utilized our method to show the presence of an antibody to tumor antigen in animals bearing transplanted tumors. Shevliaguin (24), working at the Institute of Epidemiology and Microbiology in Moscow, employed the method we used and presented evidence for the specificity of antigens found in the blood plasma of rabbits with Brown-Pearce carcinoma. Gordilowa *et al.* (25), by the same approach (*in vitro* anaphylaxis with desensitization), were able to prove the presence of specific antigens in the serum of patients with malignant neoplasms. Grace and Lehoczky (26) offered further proof of the usefulness of the Schultz-Dale test in demonstrating antigenic differences between tumor and normal tissues. Hackett and Gardonyi (27) reported further experimental proof in support of our finding of cancer antigens.

Since tumor homogenates are antigenic, there is a tendency to think of the immunologic composition of a tumor in terms of antigens only. In this paper we shall attempt to show that both antigens (auto-antigens) and antibodies (auto-antibodies) are present in neoplastic tissues and in tissues from some other diseased states.

In our early work we immunized guinea pigs with a cancer antigen obtained from cancer tissue homogenates, and then used excised uterine horns (coated with antibody) in a Schultz-Dale bath. The anaphylactic reactions were released by the addition of serum from a patient with carcinoma, following desensitiza-

tion of the same uterine segment to normal serum. Since a dynamic interaction takes place between the tissues and the blood, presumably the presence of these circulating antigens in the blood reflects the presence of fixed antigens in cancer tissues. In another paper (19) we reported the release of the Schultz-Dale reactions by the use of homogenates from cancer tissues similar (but not identical) to those used for the immunization of guinea pigs. This indicated, in a direct way, the presence of active antigens in tumor tissue homogenates. This phenomenon, however, was not consistently observed and was much harder to elicit with the mitochondrial fraction I (M-1) than with the microsomal fraction (m).

As a result, several questions arose: Why is it that the mitochondrial fraction I (M-1) is effective *in vivo*, when injected into guinea pigs to immunize them, but is not effective in most instances when used directly to release the Schultz-Dale reaction *in vitro*? Could it be that the reactive sites on the immunologically active units are covered and require proteolytic enzymes for "unmasking" and activation, such as are found in inflammatory cells (28, 29) around the site of injection with adjuvants? Could we, by this activation, succeed in "unmasking" active antigens or perhaps even antibodies from an immunologically inactive sediment? If so, could we not use the same sediment as a source of antibody to coat the uterine muscle *in vitro* and as a source of antigen to release the reaction? Such an approach might provide a direct *in vitro* method for detecting auto-antibodies and auto-antigens in tissue homogenates. It might also help to elucidate a number of unsolved problems regarding the mechanism of formation of such chronic diseases as cancer. The purpose of this investigation is to report on the finding by this method of auto-antibodies and auto-antigens (to be referred to collectively as auto-immune units) in homogenates from cancer tissues and from tissues of subjects with other diseases.

METHODS

This study comprised an analysis of 54 tissue specimens (obtained at biopsy or autopsy) from 17 subjects with proven malignant tumors, benign tumors, or other diseases. The latter group included patients with acute hemorrhagic pancreatitis, Parkinson's disease, myocardial infarction, and several newborn infants (including twins, one of whom had an interventricular septal defect).

From each of these tissue specimens, 20 per cent homogenates (by weight) were prepared with the use of a Lourdes homogenizer run at 8000 r.p.m. for thirty minutes while the homogenizer cup was immersed in ice.

Three fractions were prepared by differential centrifugation as follows: The homogenate was centrifuged at −5°C. at 3200 r.p.m. (equivalent to an R.C.F. of 1.5 Kg. per *g*) for thirty minutes and the sediment discarded. The resultant supernatant was then centrifuged for thirty minutes at 4000 r.p.m. (equivalent to an R.C.F. of 2.3 Kg. per *g*), and at 10,000 r.p.m. (equivalent to an R.C.F. of 10.3 Kg. per *g*). The former sediment was referred to as mitochondrial fraction I or M-1, and the latter sediment was called mitochondrial fraction II or M-2. Both were diluted with isotonic sodium chloride to amounts equivalent to the original volume of homogenate. The final supernatant (after removal of both mitochondrial fractions) is referred to as the microsomal fraction, m.

Each of these fractions was then either left untreated or was trypsinized for thirty minutes at 37.5°C. by the addition of 5 mg. of trypsin[1] (in 0.25 ml. of isotonic sodium chlo-

[1] The trypsin was salt-free, twice crystallized, prepared by Mann Research Laboratories according to the method of Kunitz and Northrop.

ride) to 0.5 ml. of tissue fraction plus 1.75 ml. of Tyrode solution. Both untreated (0.5 ml. of tissue fraction plus 2 ml. of Tyrode solution) and trypsinized fractions were used as sources of antibodies (for the *in vitro* coating of uterine segments) and as sources of antigens (to release the local anaphylactic reactions).

Each experiment was set up as follows: The two uterine horns were removed from a healthy, unsensitized guinea pig. Each of these horns was cut in half (a total of 4 segments). Segments 1 and 2 comprised the sources of antibodies for coating the tumor homogenate fraction, either left untreated (as in Segment 1) or trypsinized (as in Segment 2). Segments 3 and 4 were coated with the homogenate fraction obtained from a nontumorous subject, and either left untreated (as in Segment 3) or trypsinized (as in Segment 4). All 4 segments were then coated with antibodies *in vitro*.

Coating was accomplished by immersing the uterine segment in a mixture of tissue homogenate fraction and Tyrode's solution surrounded by crushed ice (−5°C.) for one hour, with air bubbled through the mixture during the period of contact.

Each of these 4 coated uterine segments was then used in a separate Schultz-Dale bath (18, 19) containing Tyrode's solution with half-strength calcium and a tenfold concentration of magnesium (30).

To release the *in vitro* anaphylactic reactions, the same 4 tissue fractions used for coating (as sources of antibodies)were also added to the Schultz-Dale baths as sources of antigens. Additions (in 1-ml. amounts) and readditions (without washing)of the untrypsinized nontumorous fraction as antigen, were continued until a significant contraction (Contraction Index_{1000} of more than 100) occurred or until a total of 4 ml. of undiluted homogenate was used. The baths were washed several times with Tyrode's solution. The trypsinized nontumorous fraction was added (in 1-ml. or 2-ml. amounts) and re-added (without washing) until the muscle manifested a significant contraction (C.I._{1000} of more than 100) or until the amount of trypsinized antigen used was equivalent to that of the undiluted and untreated antigen (the dilution factor being taken into consideration).

After washing with Tyrode, the untreated tumorous fraction was added to all 4 baths, followed by washing and then by the addition of the trypsinized tumorous fraction. For comparative purposes, the immunologic activity of each homogenate was expressed as C.I._{1000} per ml. of undiluted homogenate. A C.I._{1000} value below 100 was not considered to be significant.

To each of the 4 uterine segments (whether coated with tumorous or with nontumorous homogenates) additions were made of both nontumorous homogenates (untreated and trypsinized) and tumorous homogenates (untreated and trypsinized). Each uterine segment was thus used as its own control. This enabled us to study the effect of trypsinization on the release and distribution in tissues of immunologically active components.

In addition, attempts were made to compare, from an immunologic point of view, so-called "healthy" tissues (tumor-free heart and lung obtained from a tumorous subject) with tumor tissue from the same subject, and also with homologous tissues from nontumorous subjects.

Similar comparative studies in the same subjects were also made between "normal" tissues and tissues which were the site of other pathologic lesions (the heart with a congenital defect in twin Baby A and the heart of the other twin, Baby B; and also lung tissue from both Baby A and Baby B.)

RESULTS

Since the same homogenate fraction is used both as the antibody source and the antigen source in the Schultz-Dale reaction, immunologically active components could be safely called *auto-antibodies and auto-antigens* or could be collectively known as *auto-immune units*.

In Table 1 and Figure 1, auto-immune units (A-i.U.) detectable in terms of

TABLE 1

Distribution of Cell-bound Auto-immune Units (Auto-antibodies and Auto-antigens) in 53 Tissue Fractions (Mitochondrial and Microsomal) from Subjects with Tumors and Other Localized Lesions and Also from Subjects in Whom No Localized Lesions Were Found in the Tissues Tested

(Auto-immune units (A-i.U.) are recorded in terms of $C.I._{1000}$ per ml. of original homogenate.)

Source	Fraction	Number Analyzed	Free A-i.U., Ag. Untreated, Ab. Untreated	Partially Released A-i.U.		Released A-i.U., Ag. Trypsinized, Ab. Trypsinized
				Ag.untreated, Ab. trypsinized	Ag. trypsinized, Ab. untreated	
I. *Subjects with tumors*						
A. Malignant						
1) Tumor tissue	M-1	7	156	397	1,157	1,796
	M-2	8	135	449	995	2,648
	m	3	337	522	2,468	3,497
2) Nontumor tissue (heart and lung)	M-1	2	32	104	78	667
	M-2	2	417	316	0	235
	m	1	250	463	1,530	1,640
B. Benign tumor tissue	M-1	3	7	96	2,462	4,008
	M-2	3	84	60	1,496	1,212
	m	1	0	0	0	0
II. *Subjects with localized lesions*						
A. Tissues with lesions						
1) Heart—myocardial infarct	M-1	1	652	968	646	658
	M-2	1	470	675	4,272	4,054
2) Heart—congenital defect (Twin A)	M-1	1	97	7	560	317
	M-2	1	100	891	174	1,058
	m	1	0	322	0	0
B. Tissues without lesions						
1) Heart, in case of hemorrhagic pancreatitis	M-2	1	0	184	273	438
	m	1	480	1,000	1,671	1,515
2) Lung—congenital defect (Twin A)	M-1	1	40	3	0	0
	M-2	1	57	0	76	0
III. *Subjects without localized lesions*						
A. Clinical suspicion						
1) Tissues suspected:						
a. Heart in Twin B	M-1	1	0	36	0	487
	M-2	1	0	0	0	0
	m	1	0	0	0	731
b. Lung in infant with (?) bronchopneumonia	M-2	1	568	844	0	0
2) Tissues not suspected:						
a. Lung in Twin B	M-1	1	0	0	0	0
	M-2	1	0	0	0	0
b. Heart in infant with (?) bronchopneumonia	M-1	1	0	11	0	0
	M-2	1	36	0	97	109

TABLE 1—(*Continued*)

Source	Fraction	Number Analyzed	Free A-i.U., Ag. Untreated, Ab. Untreated	Partially Released A-i.U.		Released A-i.U. Ag. Trypsinized, Ab. Trypsinized
				Ag. untreated, Ab. trypsinized	Ag. trypsinized, Ab. untreated	
B. No clinical suspicion						
1) Lung in Parkinson's disease	M-1	1	0	16	0	76
	M-2	1	0	0	0	0
2) Lung in case of inanition with malrotation of gut	M-1	1	0	21	137	18
	M-2	1	0	4	0	56
3) Heart in case of inanition with malrotation of gut	M-1	1	0	0	0	0
	M-2	1	0	0	0	0
Total		53	7,106	14,681	44,929	72,866

of $C.I._{1000}$ per ml. of undiluted homogenate are shown in terms of 1) *free auto-immune units* (when the untreated homogenate fraction is used both as the source of antigen and antibody), 2) "released" auto-immune units (when the trypsinized homogenate is used as the source of both antigens and antibodies), and 3) "partially released" auto-immune units (when either the antigen or the antibody is trypsinized while the other is left untreated).

In another publication we report our attempts to quantitate auto-antibodies and auto-antigens separately. In this paper, however, auto-antibodies and auto-antigens are collectively quantitated as auto-immune units.

Cell-bound auto-immune units in cancer

This utilization of the Schultz-Dale procedure proves to be a satisfactory method for the immunologic analysis of tissues and the demonstration in these tissues of cell-bound auto-immune units. The auto-immune units seem to be present, for the most part, in an immunologically inactive form. Treatment with trypsin "releases" these "masked" auto-immune units so that they become detectable by the Schultz-Dale procedure.

In unpublished experiments, we have found that these immunologically active units, detectable by the Schultz-Dale test and present in cancer tissues, are non-precipitating, univalent antibodies and haptens.

Both of these findings (the univalent behavior of the cancer auto-immune units as well as their "masked" nature) could explain the difficulties encountered by previous workers (31–35) and their failure to demonstrate differences by standard immunologic methods between normal and cancer cells. It also would explain the success of other workers using the Schultz-Dale test in demonstrating such antigenic differences (18–27).

By the present technique we were able to prove, for the first time, the presence in cancer tissues not only of cell-bound antigens (auto-antigens) but also of cell-bound antibodies (auto-antibodies) (Table 1). Relatively small amounts of

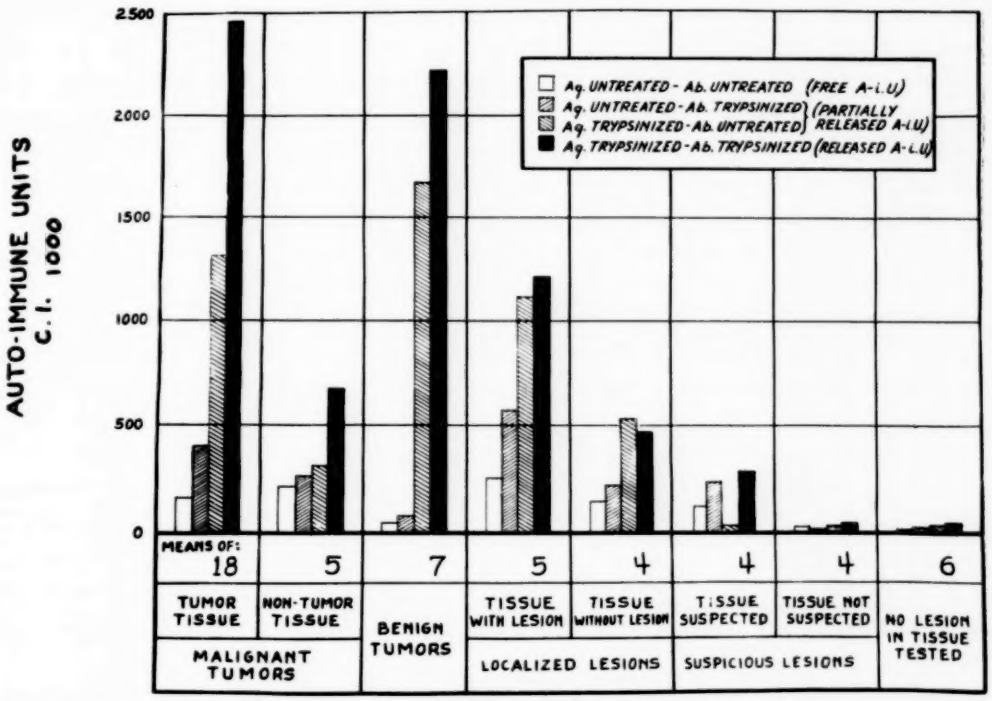

FIG. 1. Immunologic analysis of cell-bound auto-antibodies and auto-antigens (auto-immune units) in 30 fractions from tissues of subjects with tumors and in 23 fractions from tissues of subjects with other diseases. Auto-immune units (A-i.U.) are recorded in terms of $C.I._{1000}$ per ml. of original homogenate.

auto-immune units (A-i.U.) in terms of $C.I._{1000}$ per ml. of undiluted homogenate were found free in an immunologically active form in the various fractions obtained from malignant tumors, the mean values being 156 in M-1, 135 in M-2 and 337 in m, with an average of 209 Ai.U. Much larger amounts of these auto-immune units were "masked" and had to be "released" by trypsinization.

Trypsinization of tumor antibodies only, released more auto-immune units than in the untrypsinized fractions (the mean A-i.U. values being 397 in M-1, 449 in M-2, and 522 in m). Trypsinization of tumor antigens only, released even more auto-immune units (the mean A-i.U. values being 1157 in M-1, 995 in M-2 and 2468 in m). Maximal amounts of "released" auto-immune units were obtained when both tumor antigens and tumor antibodies were trypsinized (the mean A-i.U. values being 1796 in M-1, 2648 in M-2 and 3497 in m).

Both free and "released" auto-immune units were also found in the "healthy" (tumor-free) tissues from subjects with malignant tumors. Fewer auto-immune units were released, however, from "healthy" tissues as compared with tumor tissues. Although the amounts of free auto-immune units were comparable, the pattern was different in the "healthy" as compared with the tumor tissue. In the former there were no significant amounts of free auto-immune units in the M-1 fraction; in the latter all fractions had auto-immune units.

An interesting pattern was also apparent in regard to the relative distribution

of "released" auto-immune units among the various fractions studied. Thus, in malignant tumors, an indirect correlation existed between particle size and the amount of the "released" auto-immune units (the smaller the particle, the greater the amount of "released" auto-immune units). This pattern was noted in both tumor tissue and "healthy" tissue from subjects with tumors, although the amount of these auto-immune units was less in the "healthy" tissues than in tumors.

In benign tumors, however, a direct correlation existed between the particle size of the homogenate and the amount of "released" auto-antibodies—the larger the particle size, the greater the amount of "released" auto-immune units. In fact the M-1 fraction from benign tumor homogenates exhibited more than three times the amount of "released" auto-immune units than did M-2, whereas m did not contain any auto-immune units.

A dynamic interaction is continually taking place between the tissues and blood and also between tissues and other tissues via blood, and the smaller sized microsomal particles, m, are apt to travel more easily than the larger sized mitochondrial particles, M-1 and M-2, which probably are fixed to tissues. This can explain the presence of auto-immune units in the microsomal fractions (m) of malignant tumors and their complete absence from the microsomal fractions of benign tumors.

The subjects with benign tumors were capable in some manner of "locking up" these auto-immune units so that they remained well localized and well isolated from the rest of the body. In contrast, the auto-immune units in malignant tumor tissues seemed to be in communication with the rest of the body.

Thus, there seems to be some correlation between the extent to which the "released" auto-immune units from a tumor are allowed to circulate in the body and the resultant harm to the host from the tumor. There is also a correlation between the concentration of cell-bound auto-immune units (free and/or "released") and the presence or absence of a tumor.

The finding in cancer cells of both auto-antigens and auto-antibodies, as well as the evidence that these antibodies are formed *in situ* by the cancer cells themselves, suggests strongly that cancer cells are *immunologically competent cells*. This raises a significant issue which will be discussed in a separate article.

Another question of practical significance pertains to the possibility of localizing a tumor by immunologic methods. Table 2 shows the results of immunologic analysis of tumor-bearing and nontumor-bearing tissues from each of 2 subjects with carcinomatous disease. Both untreated and trypsinized mitochondrial and microsomal fractions of these tissues were studied. One of these subjects (J. M.) had a prostatic carcinoma with extension to neighboring lymph nodes, and the other (E. F.) had a recurrent carcinoma of the cervix with extension to peritoneum, bladder and rectum. Subject E. F. had been treated two years earlier by radium.

It will be seen from Table 2 that the tumor-to-nontumor (T.-Nt.) ratios of auto-immune units were low in untrypsinized fractions and higher in the trypsinized fractions. This difference was especially noticeable in the mitochondrial

TABLE 2

Immunologic Analysis of Tumor-bearing and Nontumor-bearing Tissues from Each of 2 Subjects with Carcinomatous Disease
(Auto-immune units—auto-antibodies and auto-antigens—are recorded in terms of C.I.$_{1000}$ per ml. of original homogenate.)

Subject	Tissue	Fraction	Free A-i.U. [1] Ag. Untreated, Ab. Untreated	Partially Released A-i.U. [2] Ag. untreated, Ab. trypsinized	Partially Released A-i.U. [3] Ag. trypsinized, Ab. untreated	Released A-i.U.. [4] Ag. Trypsinized, Ab. Trypsinized	Total Released A-i.U., [2] + [3] + [4]
I. *J. M.* Prostatic carcinoma; heart tumor-free	Tumor	M-1 and M-2 (mean value)	0	1,557	1,919	10,376	13,852
	Heart	M-1 and M-2 (mean value)	192	263	155	1,803	2,221
	T./Nt.* ratio		0	5.92	12.38	5.75	6.24
	Tumor	m	632	1,084	563	5,054	6,701
	Heart	m	250	463	1,530	1,640	3,633
	T./Nt. ratio		2.53	2.34	.37	3.08	1.84
II. *E. F.* Carcinoma of cervix; lung tumor-free	Tumor	M-1 and M-2 (mean values)	319	170	2,115	1,118	3,393
	Lung	M-1 and M-2 (mean values)	705	575	0	0	575
	T./Nt. ratio		.45	.30	∝	∝	5.90
Mean for both subjects	Tumor	M-1 and M-2 (mean values)	160	864	2,017	5,747	8,623
	Nontumor	M-1 and M-2 (mean values)	449	419	78	902	1,398
	T./Nt. ratio		.36	2.06	25.86	6.37	6.17

* Tumor to nontumor ratio.

fractions (M-1 and M-2) where the mean T.-Nt. ratios, for both subjects, were .36 for the untrypsinized and 6.17 for the trypsinized fractions. This represents a 17-fold improvement in the T.-Nt. ratio as a result of trypsinization. The microsomal fraction, m, exhibited a different behavior. The T.-Nt. ratio of auto-immune units for m (2.53) was higher than that for M-1 and M-2 (.36). Moreover, trypsinization of the microsomal fraction resulted in a decrease of the T.-Nt. ratio of auto-immune units from 2.53 to 1.84.

These findings are pertinent to the problem of localization of tumors by immunologic methods. In the first place, it is highly improbable that *in vivo* selective localization of tumors could be achieved by simply injecting tumor antibodies into a tumorous host. Secondly, preparation of a tumor by such an agent as trypsin (which would "release" the "masked" auto-immune units) makes the chances for selective localization to a tumor much greater. Trypsin releases a greater amount of auto-immune units from tumor tissue than from nontumor tissues, thus increasing the T.-Nt. ratio. As a result of treatment with trypsin, this effect is more marked in the mitochondrial fractions, where a 17-fold increase in the T.-Nt. ratio is obtained. Treatment of the microsomal fraction with trypsin, however, results in a 1.38-fold decrease.

Since the small microsomal fractions of tumor homogenates probably represent the circulating elements in a tumorous host which are in communication with other nontumorous tissues and which might represent the path of contamination of nontumorous tissues by auto-immune units, the fact that trypsin decreases the T.-Nt. ratio of this fraction is of definite advantage in the selective localization of tumors.

Moreover, since the larger mitochondrial fractions probably represent the elements which are more permanently cell-bound and fixed to tumor cells and which carry the auto-immune units essential for localization, it is not hard to visualize the beneficial influence of trypsin in markedly increasing the T.-Nt. ratio in these mitochondrial fractions. In this way, a dual advantage results from the treatment with trypsin.

Cell-bound auto-immune units in myocardial infarction

The correlation between the presence of a pathologic lesion and increased accumulation of immunologically active units was noted not only in tumors but also in other tissues.

Thus, heart tissue from a patient with an old myocardial infarct contained large amounts of *free* auto-immune units (652 for M-1 and 470 for M-2; mean, 561 A-i.U.) (Table 1). It also contained larger amounts of "released" auto-immune units (658 for M-1 and 4054 for M-2; mean, 2356 A-i.U.). Did these auto-immune units in cardiac tissue have a causal relationship to the lesion (*i.e.* myocardial infarction)? Is myocardial infarction an auto-immune disease?

A recent finding (36) of circulating anti-heart antibodies in rabbits without pathologic changes in the heart prompted the author to doubt the validity of the concept of auto-antibodies as a causative factor in disease. However, the fixation of circulating antibodies to tissues may be prevented by such host

factors as an antibody inhibitor (36). Riott *et al.* (37) correctly emphasized that the pathogenic auto-immune reaction may be due to the action of cell-bound antibodies. The detection by our method of cell-bound auto-immune units is, therefore, more likely to mirror the pathogenic auto-immune reaction in tissues than is the detection of circulating auto-immune units. This area is of paramount importance, and the search for cell-bound antibodies by such techniques as the one described in this article should be rewarding.

Cell-bound auto-immune units in congenital heart disease

The data on the newborn twins are shown in Table 1. In the one with the congenital heart disease (Twin A), the free auto-immune values for cardiac tissue bordered on significance (97 in M-1, 100 in M-2, 0 in m; mean, 66 A-i.U.). Twin B, with no congenital heart lesion, showed complete absence of free auto-immune units in the cardiac tissue (0 in M-1, 0 in M-2, 0 in m). The "released" auto-immune units from the cardiac tissues of both babies differed in their distribution pattern. Twin A had 317 auto-immune units in M-1, 1058 in M-2 and none in m (with a mean of 458 A-i.U.), whereas Twin B had 487 in M-1, 0 in M-2 and 731 in m (with a mean of 406 A-i.U.).

It is of interest that the free auto-immune units in the cardiac tissue of Twin A were present in the mitochondrial fractions but were absent in the microsomal fraction. Even with trypsinization, auto-immune units were released only from the mitochondrial but not from the microsomal fractions. It appears that these auto-immune units are formed *in situ* and are not transported to the heart from from some other site. In Twin B, no free auto-immune units were present in the cardiac tissue and auto-immune units were released from the microsomal fraction as well as the mitochondrial fraction M-1 (but not M-2), indicating a possible contamination of the tissues by auto-immune units formed elsewhere.

In both babies there was evidence of selectivity of the auto-immune units to heart tissue rather than lung tissue. Thus, lung tissue from Twin A showed only a negligible amount of free auto-immune units (40 for M-1, and 57 for M-2), whereas the "released" auto-immune values were 0 for M-1, and 0 for M-2. Lung tissue from Twin B contained neither free nor "released" auto-immune units.

Could the presence of such free auto-immune units in the mitochondrial fractions of cardiac tissue from Twin A explain the pathologic lesion in this baby? Could the absence of these units in the cardiac tissue of Twin B explain the absence of a pathologic lesion in Twin B?

Cell-bound auto-immune units in pancreatitis

The immunologic analysis (Table 1) of cardiac tissue from the subject with acute hemorrhagic pancreatitis showed a mean of 240 free A-i.U. (0 in M-2 and 480 in m) and about five times that amount as "released" A-i.U. (438 in M-2 and 1515 in m; mean, 977). The complete absence of free auto-immune units in the mitochondrial fraction and the relatively smaller amounts of "released"

auto-immune units in that fraction as compared to the microsomal fractions, indicates an extra-cardiac source for these auto-antibodies.

Do these high auto-immune values in acute hemorrhagic pancreatitis mean that this illness is also an auto-immune disease? Further studies in this direction are indicated.

Cell-bound auto-immune units in other diseases

What insult to a tissue is necessary before auto-immune units form? Could chronic infections result in the formation of auto-immune units? Immunologic analysis of lung tissue from a baby in whom there had been a clinical suspicion of bronchopneumonia (but no pathologic confirmation at autopsy) yielded 568 free A-i.U. for M-2, whereas the heart tissue from the same patient showed no free A-i.U. for M-1, and 36 for M-2. "Released" A-i.U., however, amounted to 844 for lung tissue (M-2 fraction); for heart tissue it amounted to 0 and 109 for M-1 and M-2 respectively. Again it is interesting to note the selectivity of the auto-immune units for the site of the suspected lesion (in this case, the lung). Although this chronic infection resulted in the production of free auto-immune units, these were easily destroyed by trypsinization *in vitro*. In this respect these auto-immune units behave quite differently from those bound to tumor cells or cells from tissues with a definite pathologic lesion.

Tissues from 2 additional subjects were immunologically analyzed by this method—lung tissue from a 74-year-old man with Parkinson's disease, and both lung and heart tissue from a 2-month-old baby with inanition and malrotation of the gut (Table 1). In all the six fractions studied, no free auto-immune units and only negligible amounts of "released" A-i.U. were found (mean, 25).

DISCUSSION

The detection of auto-immune units in tissues by this method is of both practical and academic interest.

It is the custom to view the immunologic composition of tumors in terms of antigens only. Our findings prove for the first time the presence of antibodies (auto-antibodies) as well as antigens (auto-antigens) in cancer homogenates.

These data, as well as our earlier work with the tumor skin test, introduce a new concept—that of "masked" auto-antibodies and auto-antigens (auto-immune units) which need to be released by proteolytic enzymes such as trypsin before they can be detected. Such a concept points strongly to the possibility of localization of a tumor by immunologic methods.

The finding in cancer cells of auto-antibodies and auto-antigens (auto-immune units) which are directed, not against normal cells but against cancer cells, raises some questions regarding Green's immunologic theory of cancer (38), which ascribes the neoplastic change to "antigenic" loss.

If antibodies are produced by tumor cells, they would be directed, according to Green *et al.* (39), "against cells containing the antigen they lacked—that is their normal prototypes and cells developmentally related to them" and not

against cancer cells themselves. This aspect will be discussed in more detail in another paper.

In fact, our recent finding of antibodies (rather, micro-antibodies) to amino acids and other key substances released from cancer tissue homogenates (40), may place Burnett and Fenner's theoretical concept (41) of "self" and "not self" on a more practical level.

It may be that the difference between "self" and "not self" is basically a difference in the sequence of the amino acids which make up the protein molecules. Possibly such a change in the sequence of amino acids leading to a change in molecular configuration (as might occur in this transformation from "self" to "not self") is either the result of micro-antibodies which "tie up" certain amino acids in a protein molecule or the result of a certain degree of denaturation *in vivo* of the protein molecule. Perhaps such a denaturation is brought about by repeated and prolonged contact of the protein from "self" with proteolytic enzymes shown to be present in inflammatory cells (28, 29). Could it be that prolonged contact of protein antibodies with polysaccharide antigens, which remain indefinitely in the host, may give rise to such a denaturation of protein molecules, leading to a change from "self" to "not self"?

One additional point needs to be brought out—a point which touches on the very heart of immunology. It concerns the site of formation of antibodies and perhaps also the nature of biologic specificity.

Earlier studies, reviewed recently by Harris and Harris (42), on the genesis of antibodies indicate strongly that certain specialized cells, particularly the macrophages, the lymphocytes and the plasma cells, are the source of antibodies. These studies, however, were carried out with the classic "precipitating" antibodies and do not necessarily apply to the univalent non-precipitating type, nor to auto-antibodies.

Our results concerning the site of formation of auto-antibodies seem to point in a different direction—away from the specialized cells involved in classic precipitating antibodies and towards the *in situ* formation of these antibodies by the cells (destined to become cancerous or abnormal) themselves.

These auto-antibodies and auto-antigens, which are for the most part cell-bound and masked (but are released by trypsin), are present in greater concentration (up to sixfold) in tumor tissue than in normal tissues (*e.g.*, lung or heart) elsewhere in the body. Since lung endothelium has a greater surface area and more chance for contact with blood, it should adsorb more circulating antibodies formed elsewhere as compared with tumor tissue, which is in a sense walled off from the circulation. The same argument applies to cardiac tissue which is so much more exposed to circulating antibodies than is tumor tissue. This is especially true since reactive sites on the auto-antigens of the tumor are for the greater part masked and are therefore largely unavailable for selective localization. These findings provide, therefore, an alternative hypothesis that *these auto-antibodies originated in the abnormal cells.*

This concept receives further support from a comparative study of the distribution of these auto-antibodies in the various fractions. Since the microsomal

fraction, m, represents the smallest sized particles (and the easiest to circulate), followed in size by M-2 and then M-1, one would expect that the concentration of auto-antibodies in tumors would be greatest in m and least in M-1, if these auto-antibodies are being formed elsewhere and then transported to the tumor cell. This is not the case.

In the early stages of malignant tumors the greatest concentration of these auto-antibodies was in fraction M-1, then in M-2, and least in m. In the benign tumors also, the greatest concentration of auto-antibodies was in M-1, less in M-2, and zero in m. This would implicate the tumor cells (and not any specialized cells of the reticulo-endothelial lymphocyte system) as the site of auto-antibody formation.

It may well be, as Talmage (43) states, that "antibody production is not a unique biological phenomenon but a highly specialized example of certain general cellular processes."

Our finding that both auto-antigens and auto-antibodies exist simultaneously in cancer tissue strengthens our concept that cancer is an auto-hypersensitivity disease in which the subject produces auto-antibodies against his own antibody-tumor polysaccharide complexes (15–17). Such an auto-hypersensitivity state could result from the presence of antigen-antibody complexes under certain conditions which will be discussed in another communication. Our findings also point to auto-immunity as a possible etiologic factor in myocardial infarction, in acute hemorrhagic pancreatitis, and possibly also in congenital heart disease.

SUMMARY

The Schultz-Dale method has been modified to permit detection in tissue homogenates of cell-bound auto-antibodies and auto-antigens (collectively referred to as *auto-immune units*). In this study, 2 types of auto-immune units were found: (a) *free*, with reactive sites already available for antigen-antibody interaction, and (b) "*released*", with reactive sites masked, unavailable, and requiring liberation by proteolytic enzymes (such as trypsin).

Based on data procured with this technique, evidence for the presence in cancer tissues not only of cell-bound auto-antigens but also of cell-bound auto-antibodies is presented. Evidence is also presented to show that the site of antibody formation in cancer is the *immunologically competent cancer cell.*

Cell-bound auto-immune units were discovered in: (a) heart tissue from a subject with myocardial infarction; (b) heart tissue from a subject with pancreatitis; and (c) heart tissue from a baby with congenital heart disease. No cell-bound auto-immune units were found in lung tissue from a subject with Parkinson's disease nor in lung and heart tissue from a baby with inanition and malrotation of the gut.

This approach is of great help as a tool in the study of auto-immune disease.

Acknowledgment

The author wishes to thank Mr. Edward J. Dailey, Jr., for his kind editorial assistance.

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PSYCHOLOGIC STUDIES IN NEUROLOGIC DISEASES—A REVIEW: PARKINSON'S DISEASE AND MULTIPLE SCLEROSIS*

MANUEL RIKLAN, PH.D.†, ERIC LEVITA, PH.D.‡ AND LEONARD DILLER, PH.D.§

Departments of Psychology and Neurosurgery, St. Barnabas Hospital for Chronic Diseases and New York University-Bellevue Medical Center, New York, N. Y.

Parkinson's disease and multiple sclerosis (hereafter referred to as P.D. and M.S. respectively) represent progressive chronic diseases of the central nervous system. A large proportion of the afflicted persons fall within the geriatric population. In each instance, the disease may result in alterations of the motor and sensory systems of the brain and spinal cord, and thus produce various abnormalities of movement and sensation. The specific etiology in both diseases is largely unknown (although continuing investigations reveal much new information concerning the pathology) and this lack of knowledge has thus far prevented the development of any specific therapy. Recently chemosurgery has been found useful in the symptomatic relief of both P.D. and M.S., specifically in alleviating certain of the associated abnormal movements (1–3). Because of the manifold neurologic symptoms, the relative obscurity of the etiologic factors, the lack of specific treatment, and the many and diverse behavioral effects of these diseases, recent years have witnessed an increase of investigations concerning their psychologic and psychiatric aspects. It is the purpose of the present review to summarize a portion of these investigations, most specifically those which may provide information concerning the relationship between psychologic factors, neurophysiologic substrata, and the resulting disease processes and symptoms. Thus, this review is not intended to be all-inclusive, but limited rather to those studies concerned directly or indirectly with psychosomatic and somatopsychologic relationships.

THE PROBLEM OF "ORGANICITY"

In psychologic studies of diseases of the central nervous system, the question frequently arises as to whether the pathologic process which culminates in the neurologic symptoms may also affect certain aspects of higher integrative functioning. Thus, several investigators have addressed themselves to the problem of "organic" mental factors in neurologic diseases. Several such studies in P.D. have revealed both intellectual and cognitive impairments in at least a portion of the patients so evaluated (4–6). In each instance, the changes were attributed

* This study was supported in part by the Sister Elizabeth Kenny Foundation; the Office of Vocational Rehabilitation of the Department of Health, Education, and Welfare; and the John A. Hartford Foundation.

† Chief Psychologist, St. Barnabas Hospital; Assistant Professor of Surgery (Clinical Psychology) New York University Post Graduate Medical School.

‡ Research Associate, Department of Psychology, St. Barnabas Hospital.

§ Coordinator of Training and Research in Psychology, Institute of Physical Medicine & Rehabilitation, New York University Medical Center.

to the effects of brain lesions. In studies on intellectual and cognitive functioning in M.S., there appears to be more divergence in results. On the one hand, Diers and Brown (7) reported that there were no apparent changes of a mental nature attributable to cortical pathology in their group, as based upon the results of intelligence tests. Baldwin (8) stated that in M.S., deterioration of an organic mental nature may or may not be present. Other investigators, however, found evident mental alterations, though in varying degrees (9–11). Brown and Davis (9), presumably on the basis of clinical assessments, reported that 90 per cent of their M.S. patients exhibited "mental aberrations." They distinguished symptoms attributable to the nature of the organic lesions from those attributable to the patient's personality.

In a series of studies based primarily upon administration of the Rorschach test, Kral and Dörken (12, 13) investigated certain emotional effects of brain lesions in neurologic diseases. They reported that in groups of neurologically diseased patients demonstrating subcortical or diencephalic lesions, there was a complete absence of color responses, and that such lesions result in impairment of emotional expression. They thus hypothesized that brain lesions may exert specific influences on personality functioning, dependent upon the particular localization. Moreover, they suggested that the neurotic symptoms frequently seen in P.D. have their basis in the particular localization of the brain lesions found in this disease. Teitelbaum *et al.* (14), studying an M.S. group, were unable to correlate psychic disturbances with any localized lesions in the central nervous system. In addition to changes of an intellectual or emotional nature, several types of psychiatric syndromes have been reported in patients with neurologic diseases. Schwab *et al.* (15) described 4 types of psychiatric aberrations found in groups of P.D. patients. Included were the "paroxysmal psychiatric disorders," which are of unique interest in that they may comprise formes frustres of psychoses and neuroses and thus may afford an opportunity for study of the neural correlates of certain types of mental disorders. Cohen and Gavigan (16) and Howes (17) also reported instances of psychiatric manifestations associated with neurologic diseases, specifically M.S.

The literature concerning the intellectual and emotional effects of the brain lesions found in P.D. and M.S. indicates conclusively that such changes can and do occur. Whether these are found by a particular investigator would seem to depend in part upon such factors as the specific group under consideration, the age of the patients, the length and severity of illness, or the degree of incapacitation. Moreover, the types of instruments used in assessment and the adequacy of the control groups are crucial factors. Indeed, some of the investigators do not mention the use of any controls, and the findings must therefore be open to question. The hypotheses of Kral and Dörken concerning the relationship of brain lesions to specific aspects of psychologic functioning demand further investigation and corroboration. One hesitates to accept their rather broad generalizations and conclusions when the findings concerning emotional expression appear to be based solely on one test, particularly since the validity and meaning of color responses in the Rorschach test are under considerable dispute.

PERSONALITY PATTERNS

Differentiated from investigations oriented toward the evaluation of psychologic changes due to organic lesions in neurologic diseases, are a series of studies more directly concerned with describing the personality patterns of the afflicted patients without direct emphasis on the role or roles of the neuropathologic changes themselves.

In a recent study, Machover (18) administered the Rorschach test to 30 parkinsonian patients with varying lengths of illness. He found that those with the shorter histories demonstrated rather heterogeneous personalities, but those who had the disease for a longer time tended to become more homogeneous. It was suggested that P.D. imposes a standard pattern of symptoms which may alter self-image and adaptive possibilities, thus producing ways of thinking, feeling and acting in the direction of constriction, rigidity and inertia. Diller and Riklan, in a series of studies concerning psychologic aspects of P.D. (6, 19, 20), failed to confirm the foregoing reported results. Rather, they found a wide range of personality patterns and syndromes. Although some of the patients could be described as dependent and passive as well as constricted in personality pattern, this particular syndrome did not seem to be related to length of illness. Indeed, there was some indication that when all other disease variables were taken into account, the patients with longer histories seemed somewhat better adapted.

A rather large body of psychologic studies exists on the personality of the M.S. patient. In general, the data may be dichotomized into those based upon projective or objective psychologic evaluation and those derived from clinical and diagnostic interviews. In the former category are a series of investigations by Harrower (21, 22), based upon results of Rorschach test. She describes the M.S. patient as being characterized by resignation, acceptance, and a "need to excite sympathy." This pattern she attributes to a premorbid personality structure, although psychologic characteristics alone are not considered sufficient to predispose an individual to the disease. The more advanced the disease process, the greater the constriction, dependency, and disregard for bodily symptoms. Burgemeister and Tallman (23) also reported a "weakening of the personality structure in M.S.," and Blatt and Hecht (24) found that about 50 per cent of their group of 21 subjects demonstrated Rorschach patterns suggestive of an hysterical personality. The latter investigators believed that a differential diagnosis between M.S. and hysteria is a misleading one, as the hysterical personality structure is consistently associated with the disease itself. Similarly, Canter (25) and Shontz (26), both of whom administered the Minnesota Multi-Phasic Personality Inventory to groups of M.S. patients, found high levels of self-concern, body anxiety and depression, pointing to a pattern of hysteria. One is impressed by the rather general (*i.e.*, vague) personality characteristics frequently attributed to the neurologic groups, as derived from test results. Possibly projective tests, as currently interpreted, are not sufficiently rigorous to provide the specific and concrete data necessary to differentiate these groups from other chronically disabled and neurotic groups.

Several investigations with a psychiatric orientation have been carried out

with regard to the personality of the M.S. patient. As based upon observations of 199 such subjects over a period of eleven years, Langworthy *et al.* (27) concluded that "euphoria is not necessarily the predominant mood reaction" in M.S. This particular finding is in contradistinction to the conclusions of Cottrell and Wilson (28), who evaluated some 100 patients with disseminated sclerosis. They reported that 84 per cent of the group were optimistic beyond their functioning abilities, and that 63 per cent exhibited a "frank emotional euphoria." They believed, as did Blatt and Hecht, that this type of affective symptom is characteristic of the disease and independent of duration, degree or clinical type. Thus, such symptoms may allegedly aid more in the diagnosis than does the neurologic symptom complex itself. Sugar and Nadell (29) also observed that increased optimism or cheerfulness is characteristic of M.S., and is related to the patient's previous personality make-up as well as to the possible loss of inhibitory mechanisms. Grinker *et al.* (30) reported that the M.S. patient lacks interpersonal closeness, is emotionally passive, and demonstrates minimal fantasy, repressed resentment and the absence of "free" anxiety; moreover, he exhibits great dependency and a childlike reaction to others.

In summarizing findings concerning the personality patterns of the M.S. patient, the consensus is that affective changes usually are present, most specifically in the direction of increased emotional reactivity. Moreover, an "hysterical" personality pattern is frequently described. Whether euphoria itself is characteristic of the disease remains an unresolved question. The P.D. patient has been described as "constricted, dependent and passive," but no valid pattern of personality has yet been established. Although the emphasis in the preceding studies has been on the current pattern of personality, most of the investigators have stressed the role of the premorbid personality in the patient's reaction and adjustment to the disease processes. There appears to be agreement that whatever uniformity a neurologic disease tends to impose on an afflicted patient, there will be individual variations dependent upon the previous personality pattern. Unfortunately, most test-based studies do not permit an adequate appraisal of the premorbid personality of the neurologically diseased patient, and clinical investigations are subject to numerous distortions in this area.

PSYCHOTHERAPY

The vast number of emotional concomitants to P.D. and M.S. have induced certain investigators and therapists to carry out psychotherapeutic programs with these patients. The psychotherapeutic approaches to both neurologic diseases may be described generally as supportive in nature. Langworthy (31) recommended supportive psychotherapy as defined by the development of positive interests which he thought would help to make the patient's situation more tolerable. He believed that psychotherapy is an "empirical experiment" which has not yet proved itself. Others have carried out similar studies in M.S., with both an investigatory and therapeutic orientation (32–35). In most instances, the investigators reported some therapeutic gains and recommended the continual exploration of psychotherapy as an adjunct to the management of the

neurologically disabled. However, the gains were usually rather limited in nature. Long (34) reported that in group therapy with his M.S. population, "the common disease hindered the group process by serving as a strong resistance which was never resolved satisfactorily." Yet group therapy seems to be preferred over individual therapy, since the disease similarities assist the patient to become integrated with the group.

The data are more limited concerning the psychotherapeutic management of the patient with P.D. Here again the primary orientation is of a supportive nature. Brock (36) and Chafetz (37) both recommend psychotherapy as adjuncts to the treatment of P.D.; Chafetz, in particular, indicates that psychotherapy can contribute toward assisting the patient in his over-all adjustment. Even when dealing with the neurologically diseased person in a medically oriented rehabilitation program, intensive efforts must be made in the social and psychologic areas as well as in the physical area "if significant benefit is to be anticipated from the rehabilitation program" (38). Moreover, it is clear that personality factors are significant even in drug programs for the neurologically diseased. Freudenberger (39) found that P. D. patients who are hostile, dominant and active tend not to improve with drug treatment, whereas patients who are more submissive, affectively related and inactive tend to improve. Rarely have psychotherapeutic programs with the neurologically diseased utilized control groups, thus making it difficult to assess both their therapeutic achievements and their potential for the management of such patients. Moreover, the gains made can usually be expected to be superseded by the progression of the disease process itself.

PSYCHOLOGIC ANTECEDENTS

With the continuing failure of medical science to discover the specific etiology of P.D. and M.S., a natural development for those interested in the psychologic and psychiatric aspects of the diseases has been to seek possible psychogenic factors which may bear upon the process and the symptoms. In recent years, several investigators have concerned themselves with the role of possible psychologic antecedents. Many of their studies have been psychoanalytically oriented. In such an early approach to P.D., Sands (40) reported that a "peculiar type of personality" characterizes those in whom the syndrome later develops. He describes this group as the "masked personality" and suggests that such persons are of normal or superior intelligence, pursue a path of conduct which is socially approved, and may be described as virtuous and law-abiding. However, "within," they are "always in a state of emotional tension," constantly brooding and worrying. Thus, they suppress and repress their emotional reactions and this, then, comprises the basis for their masked personality. Sands' findings appear to be based upon clinical examination of a limited number of patients whom he had followed for varying lengths of time. Others have been more intensive in their search. Such an investigator is Booth (41, 42), who carried out a series of studies in Parkinson's disease based upon several sources of evidence including the individual history, social, cultural and biologic factors, projective test results, and neurologic considerations. He describes the P.D. patient as one characterized

by an "urge toward action, industriousness, and motor activity, striving for independence, authority, and success within a rigid, usually moralistic behavior pattern." This personality structure is reportedly due to constitutional or hereditary predominance aggressiveness, a functional prevalence of the locomotor function, a tendency toward identification with a dominant parent figure, and responsiveness to social values. Booth feels that the disease symptoms appear when these personality attitudes cannot be carried on successfully. Such activities supposedly solve the dominant needs of the P.D. patient on a symbolic level, *e.g.*, by compulsive activity of the motor system and rigidity of behavior. Jelliffe (43, 44) has similarly attempted to explain certain symptoms demonstrated in P.D. He believes that the oculogyric crises and peculiar body posture are related to personality mechanisms, and that unconscious hostility, not expressed in conscious action, represents the primary souce of these symptoms. The parkinsonian body posture expresses an attitude of involuntary defense against these hostile impulses. On the other hand, the M.S. patient is described by Jelliffe as exhibiting "marked psychosexual fixations at very early stages of oedipal conflict" (45). Such repressed action patterns may result in "visceral-nerve-arc tensions," which eventually result in neurologic disturbances. Langworthy (46), in a similar though less extremely psychogenically oriented study, reported that M.S. patients are characterized by a "neurotic relationship with their mothers, passiveness in interpersonal contacts leading to hostility, and a pre-adolescent level of emotional functioning." However, he recognizes the absence of known etiologic factors in the disease.

In contradistinction to the foregoing studies, which are clearly psychogenic and psychoanalytic in nature, there are a few studies concerned with the psychologic antecedents in neurologic diseases, but they are oriented somewhat differently. These particular investigators explored the patient's early history and development for data which might be of interest, either as contributing to the disease process or as factors involved in reactions and adjustment to the disease. Diller and Riklan (6) interviewed more than 100 P.D. patients, and found that a large proportion seemed to have undergone early traumatic experiences, most significantly the death of a parent or the breakup of the family while the patient was yet a child. Moreover, many of the group reported their childhood to have been unhappy, and made negative statements concerning their attitudes toward their parents. Specifically, almost twice as many patients regarded their parents negatively as regarded them positively. As a group, the patients were closest to their mothers and in many cases the mother figure was reported to be the dominant one in the family. It was hypothesized that these factors might contribute toward the development of a weak ego structure. The studies of Braceland and Giffin (47) represent what may be described as an interactive approach to neurologic disease entities. Based upon the results of clinical examination in 75 M.S. patients of various ages and with differing severity of symptoms, they concluded that the disease "does not put a specific characterologic imprint upon the personality organization of the individual patient, but that, rather, the reverse is true." They suggest that the patient reacts to his

neurologic disease in a manner which depends upon his previous personality make-up. This reaction is modified by such factors as the severity of the neurologic disease, the social importance of the incapacity of the patient, and the economic, marital and environmental significance of all of these factors to him.

In review, investigations concerning the possible psychologic antecedents in neurologic disease range from those having a strict psychoanalytic and psychogenic orientation to those which assume a neurologic basis but which are concerned with the psychologic factors that may influence the patient's reactions to the disease process. This latter group may be referred to as somatopsychologically oriented. In studies which take a psychoanalytic approach to the neurologic diseases and their symptoms, questions concerning sampling, methodology and validity immediately arise. Although in certain instances these studies are unique and demonstrate a high degree of creative understanding, they are frequently deficient with respect to experimental design. Many are based upon extremely small samples, and all are lacking in appropriate controls. Therefore, the data presented and conclusions offered do not necessarily have generality or applicability to the population under analysis. Moreover, the data do not permit of objective or statistical analyses, and frequently are based upon intuition, individual insights, and on occasion, wishful thinking. For these reasons, one would hesitate to accept the authors' conclusions without further validation.

THE ROLE OF STRESS

If in P.D. and M.S. there are presumed to be certain relationships between the psychologic antecedents and personality patterns on the one hand, and the neurologic disturbances and symptoms on the other hand, one is disposed to seek possible sources of interaction between them. The concept of stress has been utilized by several investigators to explain, in part, the mechanisms through which this interrelationship may take place. Schwab and his associates (48, 49) have long emphasized the role of stress in P.D. Most of these patients, they believe, can be classified according to 3 primary personality types: 1) normal, stable and easy-going; 2) suggestible and dependent; and 3) driving, restless and assertive. Their clinical studies revealed that persons in the first category had a low incidence of exacerbation of disease by stress, whereas those in the second group had a somewhat higher incidence, and those in the third group had the highest incidence. Moreover, the first two groups responded well to medical therapy, whereas the third group responded less favorably. Schwab *et al.* stated that psychologically-induced stresses, through overstimulation of the vegetative nervous system (particularly the sympathetic), might produce chronic or irreversible changes in the small vessels of the mid-brain and basal ganglia. Supportive experimental data for such a view were not presented. However, it is the position of these investigators that psychologic stress plays a significant role in the development of symptoms, even though P.D. cannot be described as psychogenic in nature.

Similar hypotheses for M.S. have been proposed. Brickner and Simons (50) claim that there is sufficient evidence to indicate a relationship between stress

and the precipitation of attacks. Emotional factors are important to these authors, although they do not consider the disease to be psychogenic. Grinker *et al.* (30) also emphasized the role of stress in precipitating symptoms in the M.S. patient, who may be so precariously balanced both psychologically and physiologically that a sudden stress or change in surroundings can lead to a gradual demyelinization. Diller and Riklan (51) made a psychologic study of a group of P.D. patients about to undergo brain surgery, based on the results of a series of psychologic tests. They reported that patients demonstrating a poor response to stress in the preoperative tests tended to maintain a poor mental and emotional status during the immediate postoperative period. It was therefore suggested that even in the surgical therapy of P.D., the patient's response to stress is of significance.

APPROACHES TO NEUROPSYCHOLOGIC INTERACTION

In reviewing a series of investigations concerning the psychologic and psychiatric aspects of neurologic diseases, specifically P.D. and M.S., one is continually impressed with the implicit, if not explicit, suggestion that some form of neurologic and psychologic interaction occurs. The possible role of stress in this area has just been outlined. However, there is a wide divergence of opinion concerning the level at which such interaction may take place, and in what specific manner. Currently, there would appear to be 3 primary approaches to the investigation of neuropsychologic interactions in neurologic diseases.

1. One series of investigations is essentially somato-psychologic in viewpoint. A perhaps somewhat extreme instance of this approach is that of Kral and Dörken (12, 13), who believe that specific lesions may result in impairment of specific psychologic function. Less rigorous positions have been taken by most other investigators with this general orientation (4, 5, 10, 11, 20). The basic approach of this group is based upon the assumption that the neurologic damage in such diseases may also result in various alterations of psychologic functioning. The eventual goal of this form of investigation seems to be the establishment of relationships between types of neurologic damage and patterns of psychologic aberration. However, few specific hypotheses concerning localization of higher-level integrative functioning within the central nervous system have been presented.

2. The interaction approach to the problem of neuropsychologic relationships has been taken by some investigators (9, 29). This group suggests that changes in intellectual functioning, personality and behavior are a result of the organic lesions and/or factors in the premorbid personality make-up; the disease acts upon the personality, and in turn the personality reacts upon the disease. In summarizing the philosophy of these investigators, Braceland and Giffin (47) state "The individual as a whole reacts to his disease in a manner which to some degree depends upon his personality make-up."

3. The psychoanalytically oriented investigators approach the problem primarily from a psychogenic viewpoint (41–45). In each instance, the feeling is that unconscious psychodynamic factors play a significant etiologic role both in the

pathology of the disease and in the development of symptoms. A somewhat less rigid approach within the same general orientation is taken by Grinker *et al.* (30), who assume that a combination of psychodynamic factors may place the patient in a precarious psychologic and physiologic balance, so that a sudden change in the surroundings may lead to neurologic lesions and eventually development of symptoms. Schwab and his associates have emphasized the role of stress as a possible medium through which neuropsychologic interaction may take place.

In spite of the relatively large amount of literature in the area, very few definitive and reliable data exist concerning the role of psychologic functions in neurologic diseases. It would seem sufficiently apparent that neurologic lesions may and do eventuate in psychologic alterations. Moreover, it is probable that personality and other psychologic factors play a significant role in the patient's over-all reaction to a neurologic disease. There is also some evidence, although tenuous, that psychogenic factors play a role in etiology and in the development of symptoms. However, to date, little more than hypotheses and guesses have been promulgated concerning the mechanisms through which such interaction takes place. It would seem that the future course of investigation in this area first must be directed toward establishing more clearly the existence of such relationships and studying the specific modes of interaction.

SUMMARY

Recent investigations concerning psychologic and psychiatric aspects of Parkinson's disease and multiple sclerosis have been critically assessed. Since these studies were focused on several areas, they are discussed under the following headings: 1) "organicity", 2) personality factors, 3) psychotherapy, 4) psychologic antecedents of neurologic diseases, and 5) "stress." Three modes of approach to various problems are suggested, namely, somatopsychologic, psychogenic, and interactive.

Despite the large number of reported studies, the findings lack reliability and objectivity. More careful design and adequate methods of control are necessary if future studies involving neurology and psychology are to have general application and validity. There is great need for further data concerning psychologic and neurologic interaction in Parkinson's disease and multiple sclerosis.

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THE CARE OF THE AGED AND INFIRM IN NORWAY. A STUDY BASED ON A RECENT TRIP

M. L. RICCITELLI, M.D.*

New Haven, Connecticut

The present social structure in Norway is the product of a gradual evolutionary change extending back over many centuries since the time the Viking ships first made their appearance in the waters of the Northern countries of Europe. Since then social policy has developed mainly on the basis of trial and error and has followed no definite or preconceived plan. In the medieval era, the feudal system which formed the main framework of urban economic activity, provided the working man with a certain degree of security which continued on into the agricultural epoch. The subsequent industrialization of Norway, which started around 1865 or so, formed the basis of a greatly improved standard of living but this was bought at the price of increased insecurity for the individual. More and more people began to exchange their peaceful and secure life of the farming communities for the more strenuous, unhealthy and insecure life of the industrial centers. Within three generations that part of the population which made its living mainly from agriculture declined from about 78 per cent to about 25 per cent while the group employed by industry soared from about 12 per cent to about 60 per cent. Today Norway's extensive fisheries and merchant marine play an important role in her economy. In addition to this, industry now absorbs more than 33 per cent of the working population.

With progressive mechanization and with the steadily mounting population came the ever increasing social problems related to unemployment, sickness, accidents and old age. In 1945 Norway finally made relief the legal right of the aged, sick, crippled, mentally ill and the orphans. This responsibility became the vested rights of the local municipal poor commissions. The care of the aged and infirm thus began to pass gradually from a family to a community responsibility. The old folks were caught in the flux of a changing social tide, and the status of the grandparents, who once ruled the family group in the agricultural society, began to decline. With the coming of industrialization and urbanization, the family units were slowly disrupted and the old folks became isolated as the younger members began to migrate from the farms to the more lucrative industrial areas where there were greater opportunities. Mechanization of the farms caused a further disruption and this, together with the interplay of many other social factors, served further to isolate many of the old folks and to crystallize them into a group apart from the rest of the social structure. Thus, an ever increasing number of aged persons were left to care for themselves as best they could or to look elsewhere for assistance. Church societies, fraternal organizations and other social groups came to the rescue, but with the progressive in-

* *Address:* 476 Howard Avenue, New Haven 11, Connecticut. Assistant Clinical Professor of Medicine, Yale University School of Medicine.

crease in the old-age population the problem became so great that it was necessary to solicit more and more government aid.

NORWAY'S PROGRAMS FOR THE AGED

Today Norway has a well organized social security program which is constantly undergoing changes and improvements as the needs arise. Its basic doctrine has always been aimed at the individual approach to the problem of the care of the aged and infirm. This objective has been achieved by encouraging old people without special infirmities to live in their own homes. Special help whenever needed, and measures enabling them to live at home are being increasingly provided. Although the majority of old people in Norway today live in their own homes, either alone or with relatives, there are those who, for various reasons, are not able to do so. This group is given the opportunity to live in specially constructed dwellings provided by the local community. These homes are inexpensive and easily kept, and provide a place where special supervision and assistance can be given.

This vast program is made possible through an old-age pension which provides economic security by the allotment of an adequate income. The act provides that all people who have reached the age of 70 years and have passed a means test, together with certain other stipulations, have a right to secure an old-age pension. Persons whose income exceeds a certain amount receive either a reduced pension or no pension at all.

In addition to a basic pension, local authorities may grant a local supplementary pension under certain conditions, such as for children under the age of 18 years. The pensions are financed through a health insurance scheme and premiums are paid by all persons coming under the act, plus contributions from the local authorities, the state and the employers.

In addition to old-age pensions, there are numerous statutory pension schemes for certain occupational groups such as the State Pension Fund for Public Servants, Seamen's Fund, State Employees' Fund, Forestry Workers' Fund, and the Private Pension Fund. Old-age homes and apartments are frequently financed by private organizations. In Oslo there is the Handicraft and Industry Association's Ladies Club Home for the Aged comprising apartments for single persons and couples. There is a beautiful garden with a fountain and a special connection to a grocery store across the way. The Free Mason Home at Bygdoy has 84 apartments available for single people and couples who keep their own households and do their own shopping. It is surrounded by a park located near one of the beautiful fjords for which Norway is famous.

MEDICAL CARE

People who are acutely ill are sent to government-owned hospitals. Here they come under the care of a supervising physician. The chief of each service is appointed on the basis of a nationwide competition and, once appointed, he usually retains his position until he retires or leaves. The chief of service receives a salary and, in addition, is allowed to see private patients. Each chief of service

has two deputy chiefs and two assistants, each appointed for four years. The internes on the staff serve six or twelve months. The characteristic feature of the hospitals in Norway is that they are manned by a full-time staff for each service.

Hospital care is provided irrespective of economic circumstances. Fees are low, not only for the poor, but for the population as a whole. Payments for hospital and medical services come directly from the patients' health insurance, which now covers the entire population of Norway. This plan was put into effect in 1956, when the voluntary system was changed to a compulsory one. Health insurance pays these fees so that the population receives hospitalization and medical care free of charge.

Elderly patients with protracted illnesses but with prospects of cure or improvement are placed in special geriatric wards. These wards are attached to the general hospital and the patients are treated with the aim of restoring them either to their own homes, to nursing homes or to other institutions. Geriatric sections are furnished with all the facilities necessary for rehabilitation. This includes physiotherapy, medical and social work-ups, occupational therapy and chiropody. The most modern available equipment is used and great emphasis is placed on remedial exercises. The first of these geriatric wards was built at the Ulleval Hospital in Oslo and contained 152 beds; recently this section was expanded to 360 beds.

Old people who are chronically ill are placed in nursing homes or old people's homes. These facilities are provided for people whose infirmities have become so marked that they are no longer able to manage even with the help of the welfare services. More than half the nursing homes are equipped with special wards or infirmaries for those in need of medical care but who do not need care in a general hospital or a geriatric ward. The nursing homes are well managed and spotlessly clean. Mentally ill patients are either given care at home (if conditions warrant) or are placed in nursing homes or institutions. Other groups, such as the deaf and blind, are placed in special homes combined with infirmaries.

COMMENT

There is still a great shortage of facilities for the care of the aged and infirm, and Norway's statisticians predict that by 1970 there will be only 4 working people in proportion to each person between the ages of 65 and 70, and that the total number and percentage of elderly citizens will increase markedly. However, in spite of all this, great strides have been made and everything possible is being done to provide the elderly with a happy, comfortable and well adjusted environment. In addition, old people are being integrated as much as possible into the national industrial economy. Welfare measures are under constant appraisal and changes are made whenever necessary in order to correct existing deficiencies as they arise in the nation's welfare pattern. In this way Norway has been able to maintain freedom and welfare side by side.

OXYGEN THERAPY

OSCAR NEUFELD, M.D., F.C.C.P.*

Toledo, Ohio

The purpose of oxygen therapy is to provide and maintain a normal supply of oxygen for the blood and tissues. Factors interfering with normal oxygen gas exchange are primarily those related to mixing and dilution, diffusion, shunting and distribution.

Lack of oxygen in the blood may result from a variety of factors. There may be a subnormal pressure of oxygen in the atmosphere, as found at high altitudes. The inhaled air may not be able to get into the alveoli because of obstruction (pharyngeal, laryngeal or tracheo-bronchial) due to foreign bodies, spasm, edema, or constriction. Fluid in destroyed lung tissue may not be able to pass oxygen from the alveoli into the blood capillaries. Blood may not be able to carry enough oxygen because of a decreased amount of oxygen-carrying hemoglobin. Severely injured tissues may not be able to utilize the oxygen brought to them. Anoxemia may occur in cardiopulmonary disease because of hypoventilation or a decrease in alveolar ventilation in relation to the oxygen consumption, owing to impairment of diffusion, venous-arterial shunts (intracardiac-intrapulmonary) and uneven ventilation in relation to blood flow.

NORMAL VENTILATION

The function of ventilation is to provide adequate intake of oxygen and adequate output of carbon dioxide. This is accomplished by the exchange of gas between the atmosphere and the alveoli (ventilation) and between the alveoli and the pulmonary capillaries (diffusion), and by the transport of oxygen from the pulmonary capillaries to the body tissues, and of carbon dioxide in the opposite direction (perfusion).

The normal movements of the diaphragm and intercostal muscles provide a bellows which pumps air in and out of the lungs in sufficient quantities to supply the necessary amount of oxygen, and to remove the carbon dioxide which is produced by metabolic processes. In the normal person this action provides a fairly uniform alveolar aeration; however, a small number of alveoli may not be fully aerated, and hyperventilated or hypoventilated areas may coexist at the same time in the same patient. Interference with the bellows action of the lungs may alter the gas exchange, with resulting in defective alveolar aeration.

DEFECTIVE GASEOUS EXCHANGE

The gaseous exchange between the alveoli and the pulmonary capillaries frequently suffers from two main defects: 1) *Poorly ventilated or nonventilated alveoli*, as seen in fibrosis, atelectasis, loss of elasticity, depressed respiration, obstruction, and hyperventilation. All of these disorders restrict the free move-

* *Address:* 218 Michigan Street, Toledo 2, Ohio.

ment of the air in and out of the alveoli. (The average physician can detect this uneven ventilation by the absence of breath sounds and by the uneven movements of the chest wall, *e.g.*, in pleurisy). In this situation the partial pressure of oxygen in the involved alveoli will be decreased, and the blood perfusing these poorly ventilated alveoli will be incompletely saturated, though mixing with normally saturated blood. Carbon dioxide removal will likewise be impaired, since non-aerated alveoli cannot give off carbon dioxide. This condition is known as "venous admixture" or "physiologic shunt." 2) *Normally ventilated alveoli, but impaired or absent capillary blood flow*, as seen when the capillary blood supply is obliterated by fibrosis, thrombosis or vasoconstriction. Ventilated alveoli without blood perfusion represent functional dead spaces. Thus, the relationship of aeration and perfusion determines the mixture of gas in the pulmonary capillaries.

In various cardiopulmonary disorders in which areas of the lung are perfused but not ventilated, lack of saturation results. The normal exchange of gases in the lungs depends not only upon normal total alveolar ventilation and normal pulmonary blood flow but also upon the proper ratio between them. The average alveolar ventilation is approximately 4 liters per minute and the average normal blood flow approximately 5 liters per minute.

In the presence of normal alveolar aeration and normal capillary blood flow, anoxemia may still occur if the *diffusion of oxygen is impaired*. The surface area for gas exchange is estimated to be 90 square meters (1). Oxygen molecules, in order to reach and combine with hemoglobin, must pass through the alveolar capillary membrane, *i.e.*, the alveoli, interstitial fluid, capillaries, plasma and red blood cells. A decrease in oxygen diffusion along these structures has been found in berylliosis, pulmonary scleroderma, pulmonary carcinoma, metastasis to the lungs, Boeck's sarcoid, sulphur dioxide poisoning, pulmonary edema, pulmonary fibrosis, silicosis, emphysema, mitral stenosis, postpneumonectomy disorders, and miliary tuberculosis.

In some congenital heart defects and pulmonary arteriovenous fistulae, *shunts* are present, and the blood from the right heart is diverted through channels added to the pulmonary capillary bed and thereby deprived of contact with alveoli. The consequence is unsaturated arterial blood. In advanced pulmonary emphysema and fibrosis, many small shunts may exist whereby alveoli are almost normally perfused with blood but are not ventilated due to the alveolar destruction. Such reduced alveolar aeration results in a subnormal pressure of oxygen and, moreover, the blood which perfuses the aerated alveoli is unsaturated. Anoxemia due to venous-arterial shunts is increased by exercise because the oxygen content of shunted venous blood is lower during exercise owing to the increased removal of oxygen by the muscles.

Venous-arterial shunt is the only condition not correctable by inhalation of oxygen. Anoxemia due to hyperventilation, impairment of diffusion, or uneven ventilation can be corrected by oxygen therapy.

Blood combines with oxygen in physical solution as dissolved oxygen and in chemical combination with hemoglobin. An *inadequate quantity of hemoglobin*

per given unit of blood, as in severe anemia, impairs the transport of oxygen to the tissues. Hemoglobin may be bound with other chemical substances so that an insufficient quantity is available to carry oxygen (*e.g.*, carbon monoxide has a chemical affinity for hemoglobin 200–300 times greater than that of oxygen). Hemoglobin is no longer available for the transport of oxygen when combined chemically to form such compounds as sulfhemoglobin, carbon monoxide hemoglobin, and methemoglobin. The amount of oxygen carried in solution in the plasma during the breathing of air at sea level pressure is very small. Since a man of average size will use approximately 200 ml. of oxygen per minute at rest, it is obvious that the amount of oxygen required to meet the normal metabolic needs of the body tissues cannot be carried in solution in the plasma (2). Circulatory failure and the consequent reduced cardiac output decrease the oxygen available for the tissues, since an insufficient amount of hemoglobin passes through the pulmonary capillaries to transport the quantity of oxygen necessary for normal tissue metabolism. Shock, acute blood loss, and cardiac failure with a prolonged fall in blood pressure are the conditions that most often cause interference in the transport of oxygen from the lungs to the tissues.

INDICATIONS FOR OXYGEN THERAPY

Cyanosis is a poor and unreliable clinical sign of the need for oxygen therapy. In severe anemia, cyanosis may be impossible to recognize because of the lack of hemoglobin; also in shock, because of the marked constriction of surface vessels and the decrease in capillary blood. The blue color visible through the skin is dependent upon a sufficient amount of reduced hemoglobin; cyanosis does not appear until there is at least 5 mg. of reduced hemoglobin per 100 ml. of capillary blood. Regional slowing of the circulation or increased tissue utilization of oxygen may cause local cyanosis without anoxemia. In polycythemia there is a greater chance that this amount of unsaturated hemoglobin will be present, and the extent of anoxemia is often overestimated. Several factors such as hemoglobin content, shunts, pulmonary oxygenation and peripheral desaturation (singly or in combination), may cause cyanosis. Some of these factors may cause anoxemia, some not. Consequently cyanosis is not a reliable sign of the need of oxygen therapy.

Dyspnea, likewise, is not a reliable sign of the need for oxygen. Dyspnea has no measurable physiologic or physical basis and its significance varies from one patient to another. Many factors not related to anoxemia may cause dyspnea.

The ideal criterion of the need for oxygen therapy is the determination of the oxygen saturation of the arterial blood. Since, however, this is not extensively practiced at the present time, the pulse rate may be used as a guide. An increase in the pulse rate is the earliest and most consistent sign of anoxemia. When in doubt, an oxygen therapeutic test is helpful. If the pulse rate decreases 10 beats per minute within a minute or two after inhalation of 100 per cent oxygen, correctable anoxemia is present. The common clinical signs of oxygen want are: 1) increased pulse rate; 2) increased rate and depth of respiration progressing to rapid and shallow breathing; 3) central nervous system symptoms such as head-

ache, disturbances in vision, anxiety, and a change in attitude which may progress to delirium and coma; and 4) hypoxia of the gastro-intestinal system, leading to nausea and vomiting.

Oxygen therapy is absolutely indicated in several conditions, regardless of the status of oxygen saturation of the arterial blood. In acute coronary occlusion the immediate results of adequate oxygen therapy are sometimes dramatic. It is also effective in many cases of cerebral thrombosis, shock, carbon monoxide poisoning, allergic emergencies, labor and delivery (prevention of fetal death and brain damage), hyperpyrexia, toxemia, and hemorrhagic disorders in which the total quantity of hemoglobin is diminished. The value of oxygen therapy in these conditions is dependent upon the fact that plasma has the ability of carrying oxygen in a small but significant amount, and the amount is determined by the tension of oxygen in the inspired air. The tension of oxygen in the plasma is, in the final analysis, the important factor in tissue oxygenation, for hemoglobin does not supply oxygen directly to tissues. The volume of oxygen dissolved in the blood plasma (not carried in the hemoglobin) is only 0.3 per cent. Inhalation of 100 per cent oxygen increases the volume dissolved in the plasma.

CONTRAINDICATIONS TO OXYGEN THERAPY

Chronic hypoxia (*e.g.*, secondary to chronic pulmonary emphysema) of long standing, if treated with high concentrations of oxygen, may result in the syndrome of carbon-dioxide narcosis and respiratory acidosis. In these patients the respiratory center appears to have such a low sensitivity to the carbon-dioxide stimulus that the peripheral chemoreceptors in the carotid and aortic bodies become the chief agents for maintaining respiration, being stimulated by hypoxia. Obviously this single remaining mechanism should not be abolished or removed; otherwise, the accumulation of carbon dioxide will continue, leading to narcosis. In conditions of chronic hypoxia of long standing, cautious administration of oxygen (in a concentration not higher than 35 per cent and only for very short periods) may be of benefit, because it diminishes the work of breathing and thereby the production of carbon dioxide.

Administration of excessively high concentrations of oxygen over long periods of time (seven to twelve hours) without interruption may cause substernal distress. To avoid any such complications, concentrations close to 100 per cent should be given intermittently—preferably five to seven minutes of rest after thirty minutes of therapy.

High concentrations administered in acute conditions preceded by chronic hypoxia of long standing may also cause carbon-dioxide narcosis.

Treatment with high concentrations of oxygen for prolonged periods (ten days or longer) may cause retrolental fibroplasia in newborn infants. Oxygen therapy for premature infants should be administered in the lowest possible concentration for very short periods at a time (hourly) and with interruptions. Infants of multiple births appear to be much more susceptible to retrolental fibroplasia that those of single births.

METHODS OF ADMINISTRATION OF OXYGEN

Nasal catheter. The average concentration of oxygen delivered with this method is 30 to 38 per cent. The technique is as follows: The tip of a soft rubber catheter (French # 10 or # 12) is lubricated with water-soluble jelly (oily lubricants are contraindicated because of the hazards of lipoid pneumonia) and inserted into the nostril up to the posterior wall of the nasopharynx. Because rapidly flowing oxygen dries the mucous membranes, it should be water-humidified by passing through a humidifier attached to the oxygen tank. To supply a concentration of 30 to 38 per cent to the inspired atmosphere, an oxygen flow of 6 liters per minute is necessary. A slightly higher concentration of oxygen per rate of flow can be obtained by placing the tip of the catheter opposite the uvula, but this should be avoided because air may be swallowed and produce gastric dilatation. The catheter should be alternated from one nostril to the other at four-hour intervals. A flow of less than 6 to 7 liters per minute is inadequate, but overflow may cause discomfort. A nasal cannula is usually more comfortable for the patient than a nasal catheter, and the delivered concentration of oxygen compares favorably for the same rate of flow. A polyethylene catheter is less irritating and may be left in place without changing for at least twenty-four hours.

Face tent. The average concentration of oxygen delivered with this method is 40 to 50 per cent, using a flow of 6 liters per minute. The tent fits on the sides of the face and below the chin and has an open top for outward diffusion of exhaled gas. It is a very comfortable method of administration, since breathing is completely free, visibility is unobstructed, and the fear of being "closed in" is eliminated. Humidified oxygen enters the tent by means of a shower-head dispersal system.

Tents and hoods. The average concentration of oxygen delivered with this method, when all rules are followed to prevent undue leakage, is 40 to 60 per cent, using a flow of at least 12 liters per minute. Supplying oxygen by this means is seldom satisfactory because of the meticulous attention required to keep the tent gas-tight. The concentration of oxygen should be checked at least twice daily 1) because of possible leakage, and 2) because each time the tent is opened the concentration of oxygen drops and it takes several minutes to build it up to the desired level again. The motor-driven fan should always be turned off when the tent is opened.

Face masks. The average concentration of oxygen delivered with this method is 40 to 95 per cent, using a flow of 6 to 12 liters per minute (the flow of oxygen must be equal to or greater than the patient's minimal respiratory volume). In considering the wide variety of mask units available, it should be borne in mind that for oxygen therapy the use of a rebreathing unit is contraindicated, not only because of the accumulation of carbon dioxide but also because high oxygen tension inhibits the transportation of carbon dioxide back to the lungs. An inspiratory valve at the entrance to the face mask from the collecting bag, and an inspiratory valve in the face mask itself, eliminate the accumulation of

carbon dioxide. This arrangement of valves likewise reduces mechanical resistance to respiration.

SUMMARY

Conditions favoring defective alveolar-capillary gaseous exchange are reviewed.

The indications and contraindications for oxygen therapy are presented. Various methods of administration are described.

The equipment for oxygen therapy should be chosen in relation to: 1) the concentration of oxygen required in the particular case to saturate the arterial blood to the normal level of 96–98 per cent, and 2) the rate of ventilation required to provide sufficient alveolar aeration to eliminate carbon dioxide.

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INEFFICACY OF CAROTID SINUS STIMULATION IN ATRIAL FIBRILLATION*

WILLIAM SCHWARTZ, M.D.†

Heart Station, Fall River General Hospital, Fall River, Massachusetts

It is not widely known that early atrial fibrillation tends to revert to normal sinus rhythm spontaneously, and may often recur repeatedly for periods of a few minutes or longer.

A healthy, young subject with atrial fibrillation and no other demonstrable evidence of heart disease should be managed with great caution, for it is easy to convert normal apprehension into cardiac neurosis (1). That atrial fibrillation may occur in the absence of heart disease is well known (2). However, atrial fibrillation should be considered a definite sign of heart disease until proved otherwise, and the physician should not suggest that the patient has an organic cardiac disorder until he is sure of the diagnosis. The term "lone atrial fibrillation," in England, refers to atrial fibrillation without any evidence of heart disease (3). Because atrial fibrillation in the absence of a cardiac lesion in thyrotoxicosis or amyloidosis does not produce enlargement of the left atrium or the heart as a whole, even though the arrhythmia may have persisted for many years, 3 radiologic criteria have been postulated for the diagnosis of "lone atrial fibrillation":

1. The absence of even a moderate amount of total cardiac enlargement.
2. The absence of dilatation of the left atrium, as viewed roentgenographically after the patient has taken a swallow of barium.
3. The absence of pulmonary congestion, both initially and throughout the years.

Atrial fibrillation can cause severe cardiac failure in an otherwise normal heart, and the failure is reversible if normal sinus rhythm is restored and maintained; nevertheless, although this is well known, the diagnosis is often missed. Brill *et al.* (4) recently reported a case in which the decompensation had been reversed twenty-five years previously. Phillips and Levine (5) reported similar findings in 1949, and a case was reported by Schwartz (6) in 1960.

The following case is pertinent in this regard, and also demonstrates the inefficacy of carotid sinus stimulation in treatment:

CASE REPORT

A 73-year-old active man with paroxysmal atrial fibrillation since 1933, had no apparent cardiac disease until the fall of 1957, at which time he experienced a paroxysm of atrial fibrillation and the sudden development of congestive failure. Medication restored normal sinus rhythm, with complete reversal of the congestive failure, and this state was maintained for the next six months without medication.

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* Presented at the Staff Meeting, May 17, 1960.

† *Address:* 240 Second Street, Fall River, Massachusetts.

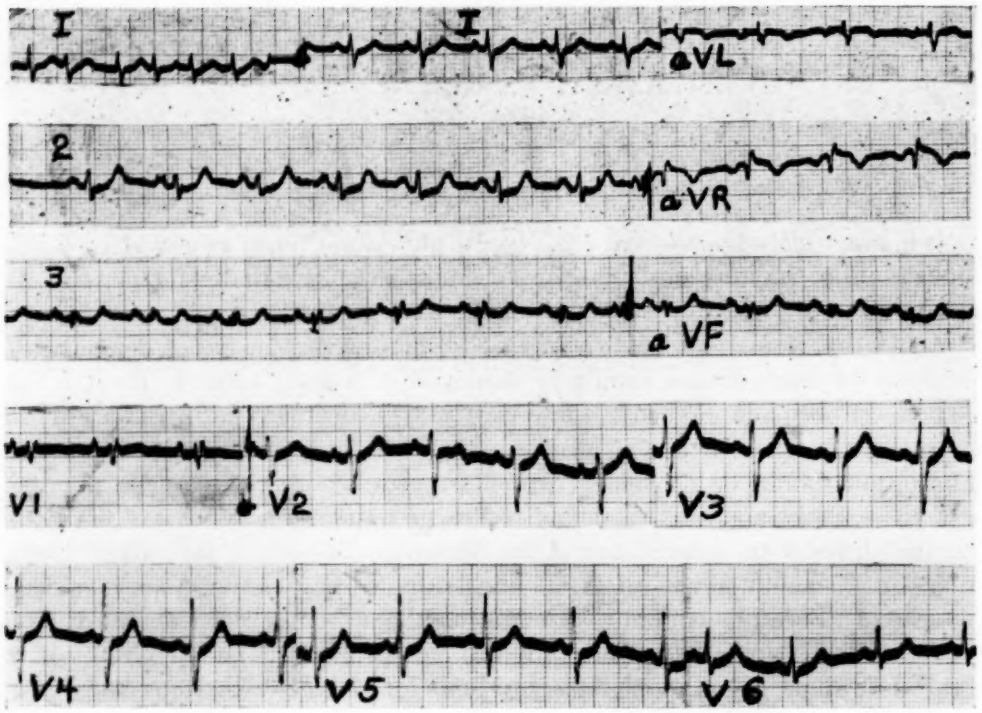

FIG. 1. Paroxysmal atrial fibrillation with a ventricular rate of 200 per minute and normal sinus rhythm in a twelve-lead electrocardiogram. There was spontaneous conversion to normal sinus tachycardia with a rate of 110 per minute in lead 1, coincidental with carotid sinus stimulation, and a further decrease to a normal sinus rhythm rate of 90 per minute in aVL and throughout the rest of the tracing.

While walking to work on a cold February morning in 1958, he again had a paroxysm of atrial fibrillation. Because of his apprehension, an electrocardiogram was obtained. Figure 1 demonstrates the atrial fibrillation in lead 1. The ECG machine was stopped, and carotid sinus stimulation was applied; there was a coincidental return to normal sinus tachycardia, and the aVL showed normal sinus rhythm. Figure 2 is a roentgenogram of the chest. The over-all dimensions of the heart were well within normal limits and the lung fields were clear; however, the left atrium was enlarged, as viewed in the left lateral position after the patient had taken a swallow of barium. Latent thyrotoxicosis was ruled out, and all other laboratory and physical findings were noncontributory.

The patient had no clinical or electrocardiographic manifestations of the arrhythmia for two years after the first recorded conversion to normal sinus rhythm. Then, while walking to work on a cold February morning in 1960, he again experienced a paroxysm of atrial fibrillation and became quite apprehensive. The author, being duly alerted, obtained a continuous electrocardiographic tracing. Figure 3A shows atrial fibrillation with a spontaneous return to normal sinus rhythm. No attempt was made to apply carotid sinus stimulation, to make postural changes, to obtain other ECG lead sequences, or to influence the arrhythmia in any other manner.

A few weeks later, while walking to work on a cold winter morning, atrial fibrillation again occurred under the same circumstances. No attempt was made to influence the arrhythmia in any way. Figure 3B shows atrial fibrillation with a spontaneous return to normal sinus rhythm.

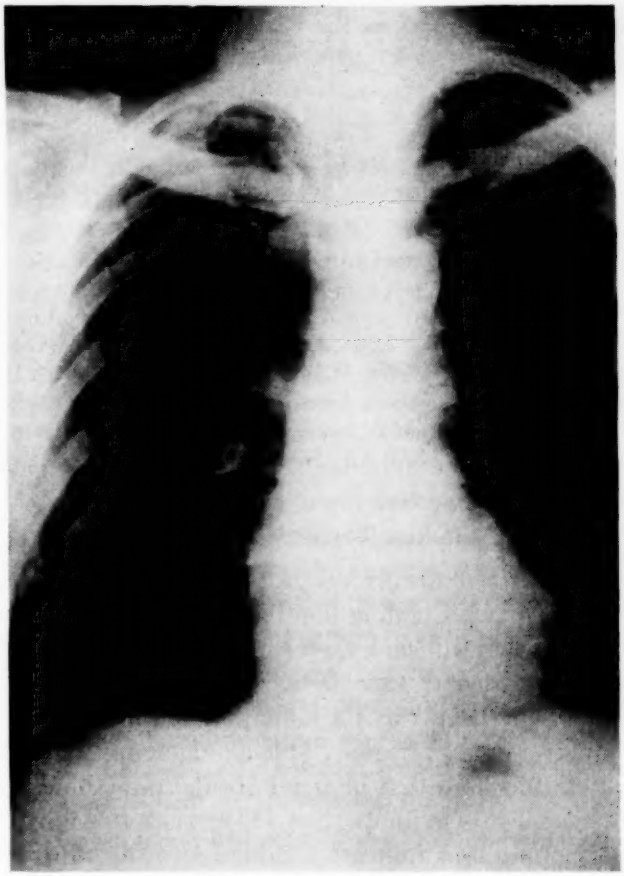

FIG. 2. After twenty-seven years of paroxysmal atrial fibrillation, the lung fields are clear and the over-all dimensions of the heart are well within normal limits.

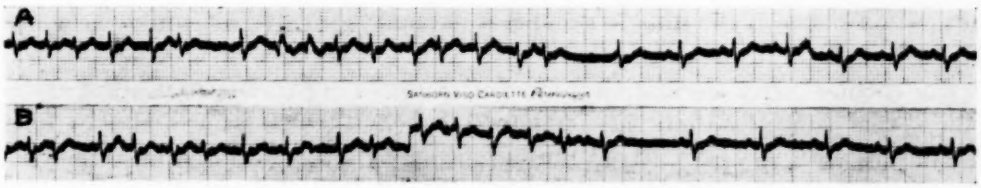

FIG. 3. **A**. Electrocardiographic tracing of lead 1, demonstrating paroxysmal atrial fibrillation with a ventricular rate of 130 to 175 per minute and spontaneous conversion to sinus tachycardia with a rate of 100 to 110 per minute, preceded by a compensatory pause of .80 second before the conversion.

B. Paroxysmal atrial fibrillation in the same patient a few weeks later. The ventricular rate was similar to that on the previous occasion, but this time there was a spontaneous conversion to normal sinus rhythm at a rate of 85 to 90 per minute, preceded by a longer compensatory pause of .96 second.

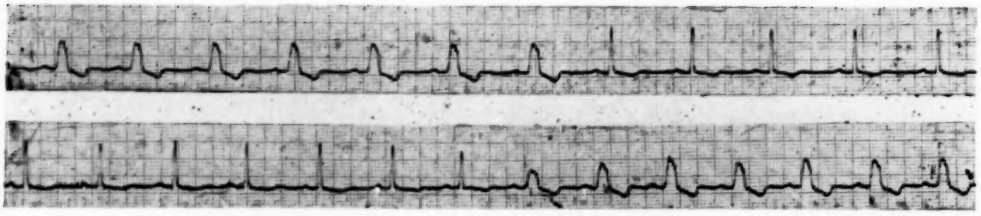

FIG. 4. A single, continuous electrocardiogram with a rate of 65 per minute (top row) showing conversion of paroxysmal left bundle branch block to normal conduction without any compensatory pause, the rate after conversion being a beat or two slower. The transition occurred spontaneously, without any carotid sinus stimulation, hyperventilation or change of body position. Normal conduction continued for half an hour, with the rate increasing to about 73 per minute; then there was a spontaneous return to bundle branch block without any compensatory pause. (From Schwartz, W.: Normal QRS interval in left bundle branch block, *J. Am. Geriatrics Soc.* **8:** 861 (Nov.) 1960; Fig. 4.)

DISCUSSION

The mechanism of atrial fibrillation is fundamentally the same as that of atrial flutter, with no sharp dividing line between the two. Gardberg (7) states that carotid sinus massage will slow the ventricular rate in atrial fibrillation, but will not slow the ventricular rate in atrial flutter. Massey (8) makes the contradictory statement that vagal stimulation in atrial flutter may produce not only slowing, but a greater degree of block, changing a 2:1 to a 3:1 conduction. Katz and Pick (9) found that in atrial fibrillation, stimulation of the vagus will slow the ventricular rate in jumps, but will not as a rule alter the atrial rate—only the ratio of the impulses that are conducted to the ventricles. Stimulation of the carotid sinus may cause a temporary slowing of the ventricular rate, but upon cessation of the stimulation the ventricular rate returns to its previous state. The electrical and mechanical manifestations in atrial fibrillation differ radically from those in any other form of atrial arrhythmia. There is no coordination between the muscle groups; some may be in systole while others are in diastole (10).

Unexplained atrial fibrillation is most often found in patients 40 years of age or older; this suggests that the tendency to maintain orderly atrial activity diminishes with age (11). Atrial fibrillation may come and go because the conductivity of the sino-atrial node is depressed but not abolished. The node is able to conduct impulses through the atrial conduction path when the cycle is long enough to permit recovery from the increased sino-atrial refractory period. A similar mechanism is observed in intermittent left bundle-branch block. In this condition the conductivity of the bundle of His is depressed but not abolished, and the bundle is able to conduct when the cycle is long enough to allow for recovery from the increased refractory period (12). Gardberg and Rosen (13) demonstrated that in a patient with an initial left bundle-branch block but no evidence of heart disease or hypertension, stimulation of the carotid sinus caused the block to convert to normal QRS conduction.

There are numerous reports in the literature of spontaneous remissions of left bundle-branch block. An excellent example of the spontaneous abolition of such a block, with a compensatory pause following the premature ventricular contraction marking the onset of normal conduction, was described by Lamb *et al.* (14). Figure 4 shows the electrocardiogram in a case of left bundle-branch block in a 60-year-old man who had an attack of acute myocardial infarction; there was spontaneous abolition of the QRS conduction defect, but no premature ventricular contraction nor any compensatory pause preceding the return to normal conduction. Carotid sinus stimulation had been applied at various intervals during the previous week, with negative results. At the time of conversion, there was no application of carotid sinus stimulation to obscure the sequence of events.

In the case reported here, carotid sinus stimulation had been applied at the time of the first return to normal sinus rhythm; however, subsequent events showed that it actually had no part in the mechanism of conversion. In retrospect, for all 3 episodes, the excitation of walking to work on a cold winter morning seemed to trigger the paroxysms of atrial fibrillation. It is possible that merely sitting in a warm room at rest may have terminated these paroxysms. In the early part of a paroxysm or in early atrial fibrillation there is a tendency toward spontaneous reversion to normal rhythm. Paroxysms appear and disappear for shorter or longer periods, as recorded here and corroborated by others (Littman, D., personal communication, April 1960).

SUMMARY

A case of atrial paroxysmal fibrillation is presented in which it was evident that carotid sinus stimulation played no role in the establishment of normal sinus rhythm. Three attacks of fibrillation occurred after similar excitation—walking to work in cold winter weather. That the first reversion to normal sinus rhythm was spontaneous despite the application of carotid sinus stimulation is shown by the sequence of events during the two later attacks. In both these instances the reversion to normal rhythm took place spontaneously without the use of carotid sinus stimulation.

Atrial fibrillation may come and go in the early stages because the conductivity of the sino-atrial node, though depressed, is not abolished. This phenomenon and the tendency toward spontaneous establishment of normal rhythm apparently is not well known.

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TREATMENT—REVIEW OF A MEDICAL CONCEPT

HARRY H. GARNER, M.D.*

The Chicago Medical School, Chicago, Illinois

When Oliver Wendell Holmes (1) wrote, "It is a physician's privilege to cure seldom, to relieve often, and to comfort always," he was unaware of the tremendous advances which were about to be made in medical treatment. Today we can aptly paraphrase his statement to read: It is the physician's privilege to cure often, to relieve almost always, and to comfort always. However, the inclination to focus our therapeutic sights on the goal of cure has tended to obscure the fact that to give a helping hand and to comfort always are ideals of which the practicing physician can well be proud. In this communication, we present a variety of concepts of treatment rather than specific processes and procedures. The dynamic significance of certain treatment concepts is likewise explored. Holmes' words serve well as a background for this approach.

Contemporary ideas of treatment are by no means completely separated from modes of thought that seem more appropriate for primitive or pre-literate societies. The early development of medicine even in civilized communities centered around a priest-doctor. The union in one person of the powers to communicate with the supernatural and to heal was somewhat disrupted by the developments in pathology, chemistry, bacteriology and other scientific achievements. Thus as treatment concepts required more and more appreciation of the biologic and physical sciences, there was a corresponding lessening in the significance of the priest element in the priest-doctor role. Many of the current developments in medical philosophy or orientation, centering around such ideas as the comprehensive, holistic or total-person approach to therapy, are attempts to find a solution for vast numbers of medical problems that are difficult to relate to chemical, structural or physiologic dysfunction. This has led to various special branchings from the mainstream of medical practice, which is "organic" in its focus. Although pyschiatric disorders associated with structural changes have been influenced in general by the concepts of treatment characteristic of medical practice, the so-called functional psychoses and the neuroses have, in addition, been considered from viewpoints which involve varying degrees of philosophic, theologic and psycho-social frames of reference. The priestly content of the priest-doctor role is more in evidence in such treatment concepts as those developed by psychoanalysis, the various psychotherapeutic schools, or existentialism. The doctor who is almost completely devoid of priestly content is personified in the physician who deals with infection and structural changes. In correcting the biochemical malfunctions of the organism he feels that the intricacies of the doctor-patient relationship are not important for treatment aside from the cultivation of a "bedside manner." The physician who does not recognize the problems of the total person may limit treatment to such a narrow

* Professor and Chairman, Department of Psychiatry and Neurology.

concept of scientific objectivity and precision by means of biochemical interventions that the priestly content is eliminated from the dual priest-doctor role. He may see himself as an efficient scientist, concerned only with the material object, and under no obligation to perceive the feelings, attitudes and social transactions of his patients, though they are "objects" too, but of a different category.

BASIC PATTERN OF TREATMENT

The basic pattern for the treatment of patients as members of a social system is the same, no matter how primitive the society or the system. The essentials are:

1) the patient's verbal or nonverbal expression of a need for help regarding a condition of ill-being or a disturbance with which he cannot cope;
2) recognition and acceptance of another person as one qualified and competent to help;
3) observations, deductions and inferences by this helper which serve as a basis for the formulation of ideas as to the cause of the illness (diagnosis) and how the patient may be healed (treatment procedure); and
4) steps taken by the potential healer which are recognized as having a therapeutic intent, and which have a therapeutic effect.

Every physician should remember that a patient, in presenting himself for care and in establishing the relationship of seeking help, responds in a manner in keeping with the tendency to transfer to the physician those attitudes and feelings appropriate to child-mother-father relationships. Another factor common to all human relationships of any kind is the desire to maintain significance, status, prestige or importance in the eyes of other persons. Sullivan (2) states, "There isn't the remotest chance that any person in this social order, and probably in any other extant in the world today, will not try to put his best foot forward." The tendency for the patient to distort his history under these two influences should be recognized by the physician, who should be alert for factors behind the scenes that may obscure the treatment needs. Within this basic pattern the idea of relating treatment to the cause or causative factors in the disturbance of health, begins to operate almost immediately.

ETIOLOGY

Cause as related to treatment has been closely associated with *removal* of the cause as a goal of treatment. Specific etiologic agents are thus related to specific treatments involving the reduction or elimination of their effects. Medicine as a science has striven to establish the kind of cause-effect relationships or stimulus-response linkages which are demonstrable in other sciences. A specific cause, known to produce a specific pathologic lesion responding to a specific treatment, represents the ideal. But at best, even when such an order of events may occur, many questions remain unanswered. In recent years, Stieglitz (3) has pointed out the multifaceted elements constituting a cause. The concepts of comprehensive medicine make treatment related to a specific cause untenable. Steiger (4) has

emphasized the use of concepts such as "proximate and approximate causes" in illness. Proximate causes are those which have begun recently as against approximate causes which have their origins in more distant time. In a patient with pneumonia, the proximate cause is the pneumococcus and the approximate cause may have been a viral upper respiratory infection some weeks earlier. An unusual exposure may have taken place at that time, *e.g.*, the patient may have spent the night asleep in the park following excessive drinking. His alcoholism in turn, may be related to many factors in his developmental history as a child as well as to a current stressful life situation. Steiger indicated the impracticality of attempts to assess or deal with all the approximate causes, and emphasized the need to consider current realistic possibilities. "One can scan with the mind's eye the various proximate and approximate causes, and decide which causes it is reasonable and efficient to treat." For instance, attempts to deal with hypertension in a very obese 65-year-old woman living a solitary life on a marginal income, by limiting the proximate cause (overeating) will almost certainly meet with defeat unless some effective substitute gratification for the eating is provided. The need to please the physician and the feeling of gratification from his praise is not as likely to be a substitute for overeating at age 65 as at age 30.

Galdston (5), in discussing the dynamics of cure in psychiatry, pointed out that the same basic concepts of causation and related efforts at cure are part of all medical practice. *Demoniacal-moral* or magical-demoniacal causes invariably called for the driving out of evil spirits as the significant therapeutic effort. Such concepts were frankly important until recently, and in a pseudo-scientific substitute form they continue to influence treatment. Patients continue to view "their" allergies, "their" arthritis, and "their" other afflictions as if a private demon possessed them in this form. *Hereditary constitutional* concepts strongly influence methods of prevention. They may encourage childlessness and abortion to prevent hereditary disease, and may also encourage nihilistic thinking about treatability. *Toxic or traumatic* concepts of etiology have been important in developing methods of prevention, immunology and industrial hygiene, in the massive search for specific therapeutic agents to combat specific injurious agents. *Correction of physiologic imbalance* (chemical, hormonal, fluid or cellular), with emphasis on replacement therapy and the restoration of homeostasis is a concept of modern medicine. *Psychologic disturbances* are closely linked with socio-environmental and cultural discontinuities and inconsistencies as a cause for illness. Psychologic approaches tend to emphasize management of the patient in terms of adaptation or prevention of illness by profound socio-environmental alterations. Psychosomatic medicine, seen as a total approach to treatment, leans strongly on the psychologic theory of etiology.

DIAGNOSIS IN RELATION TO TREATMENT

Goals in treatment

Once the etiology is determined, treatment becomes related to the physician's goals for the alleviation of suffering. Their nature, in turn, will be conditioned by

the personal values of the patient, the social values of the community, and the therapeutic values of the physician which he consciously or unconsciously uses in treating his patient. In an earlier article on goals of therapy (6), the aims of the physician were related to his social role as a healer, and were formulated for our society as: 1) to save from death, 2) to cure, 3) to remove pathologic tissue, 4) to offer symptomatic relief, and 5) to help in rehabilitation. The specific manner in which the physician functions in carrying out the treatment procedures required for the accomplishment of these goals reflects his own ethical and social values. Such values are developed in him by the impact of his psycho-social environment and the ways in which he experiences it through time. A physician reared in a life situation of deprivation might, for instance, find it difficult to urge his patient to spend money on medical care. A physician brought up in a household pervaded by superstitions and ideas of magical influence might be fearful of "hexing" the patient and thus invoking unfavorable influences by an undue optimism which the fates abhor.

Personal values of the patient may be encountered as barriers to therapeutic procedures, keeping in mind the degree to which individual freedom is permitted. Treatment of an early but malignant carcinoma of the breast may be delayed or avoided completely by a Christian Scientist. In our society the patient's individuality in this regard is respected by physicians. But should the patient's illness be more frankly suicidal, then law, custom and religion require extreme measures of interference with personal freedom. In another society, as among the Japanese throughout World War II, suicides under certain circumstances were considered by custom, religion and medicine to be an honorable resolution of an otherwise insoluble stress situation, and added luster to one's escutcheon. Social values require of the physician that he isolate the patient with tuberculosis or typhoid. The individual freedoms of that patient are therefore violated. Police power may be invoked to enable the physician temporarily to ignore the personal privileges of an uncooperative patient. A physician practicing among primitive peoples may find it necessary to accept their perception of him as something that, to him, represents a delusional system with hallucinations. They may attribute to him an unusual capacity for contact with the spiritual world so that they may rationalize the evidence of his curative powers and accord him a supernatural role in their society. In the United States, he might find himself preparing commitment papers as an expression of his concept of treatment for a patient who perceives him in this role. Goals for the patient during health and disease, the individual value systems of the patient, the social values of the system in which the patient and physician operate, and the value systems of the physician all interact in a complex manner to determine the treatment of the patient (7).

Diagnostic decisions

Diagnosis and treatment are intimately related in a continuous stream of events. The logical process of evaluating positive and negative factors and the variety of possibilities is developed into a differential diagnosis. From a formal or definitive diagnosis there emanates the application of therapeutic measures

appropriate to that diagnosis. The motivation of the patient in seeking help may not be relevant to the diagnostic decisions that are reached and the ultimate treatment. A patient's need for help may be related to a desire to withdraw from a stressful situation. Extreme hostility may engender sensations which in turn give rise to cardiac findings in the form of alterations in physiologic function; changes in the electrocardiogram may even suggest structural alteration. The real need of the patient is removal from the provoking situation and treatment by psychologic methods, but the diagnostic conclusion may lead to "cardiac" therapy (immobility in a hospital bed) as the change needed to improve the patient.

Diagnostic decisions are motivated by a complex constellation of factors influencing the physician. The need for prestige, recognition, and acclaim may lead to an emphasis on obscure and difficult diagnostic tasks. Satisfaction with having obtained good results in some special syndrome with some special agent can readily influence the diagnostic decision in a new similar case in the same direction. Neurotic fears may create blind spots about the recognition of certain illnesses, and the history may be so elicited as to bring about a non-threatening diagnosis. Personal gain or a stress factor may not be a minor determinant of the diagnosis in some cases. The busy doctor may tend to make diagnoses that are not too time-consuming in the way of treatment, and the doctor with time on his hands may find work to keep him busy in the line of more exhaustive investigations and courses of treatment.

Clearly, treatment may be unfavorably influenced by a multitude of factors which distort the diagnosis-treatment continuity. The frequency with which patients are influenced by the nonspecific treatment involved in the spontaneous doctor-patient relationship further augments the confusion. The impression is gained that, since the patient responded favorably to a specific therapeutic measure directed at a certain syndrome or symptom, the original diagnosis was valid. Cumulative experience reveals that this may not be true.

TYPES OF PATIENT-PHYSICIAN RELATIONSHIPS

After the history has been taken and a diagnostic appraisal made (8), the physician calls upon his previous experience to draw up a plan of action. The plan of action, however, must of necessity be related to the diagnosis, the condition of the patient, the available materials, the capacity of the physician to use them, and the relationship of patient and physician.

Attempts to categorize by type the patient-doctor relationships seen in medical practice have received increased attention. Stokes (9) described the prevailing categories as the dominant, peer, or humility types. Brosin (10) used such terms as superior, dominant, and passive. Rado (11), in discussing psychotherapy emphasized two basic relationships: 1) adult, either self-aspiring (capable and desirous of self-advancement) or self-reliant; and 2) childlike, either parentifying (seeking a parent) or magic-craving (seeking a magical cure).

Szasz and Hollender (12) described model designs of the patient-physician interaction which were applicable to medical practice generally. The types

they noted were: *1.* Activity-passivity; the patient is unable because of reduced states of consciousness to participate or be helpful in his own treatment, and all the activity is determined by the therapist; coma, stupor, delirium and the effects of hypnosis, are included in this category. *2.* Guidance-cooperation; the patient seeking help can participate in the activity of the therapeutic situation but sees himself as relinquishing his choice of direction or authority for decision-making to the therapist. *3.* Mutual participation; the therapist helps the patient to help himself, as in the treatment of the chronically ill and in psychotherapy.

Activity-passivity

Little need be said about treatment of the patient requiring the activity-passivity relationship. The responsibility for the patient in stupor, coma or delirium is clearly defined. The therapist takes steps to preserve life, correct the chemical, hormonal or fluid imbalance, and deal with the state of altered consciousness. There will be a need for contacts which will increase the integrative tendency of the central nervous system as soon as there is some evidence that the patient is aware of his environment. When the patient shows some response to his surroundings, human interaction should proceed on an "as if" basis, that is, communication with the patient or in his presence as if he understood and comprehended what is being said. All personnel should be instructed to behave similarly. All too often the patient's state of consciousness does not preclude his hearing injudicious or joking remarks which are questionable even in the patient's absence. When spoken in the presence of the patient "as if" he were absent because of altered consciousness, the remarks themselves or their interpretation by the patient may seriously affect his attitude toward the physician, his feelings about treatment, his cooperation, the prognosis, or the expected sequelae. In his state of helplessness, the patient may be highly suggestible to what is being said.

Guidance-cooperation

The medical treatment carried out by most physicians is characteristic of the guidance-cooperation pattern. The patient relinquishes authority to the physician with an attitude of trust and a willingness to comply. This relationship is usually the most comfortable for the physician, as it makes for special gratification and prompts him to seek out and encourage such a relationship. The dependent needs of the patient, when ill, also encourage the physician to seek out and cultivate such a relationship.

Mutual participation

The mutual participation model, in which the therapist helps the patient to help himself is usually seen in psychotherapy. The activity-passivity and guidance-cooperation models are descriptive of most doctor-patient relationships. In various phases of the mutual cooperation model of intensive psychotherapy, guidance-cooperation may be more evident than mutual participation. The kind

of maturity in interpersonal relationships that is needed for exclusive use of the mutual-cooperation model is not often present in the sick person. Whenever the maturity of the patient and physician warrant mutual participation, treatment theoretically should be best carried out according to that model. The acceptance of the physician as not only a healer of the sick but also a representative of forces that can prevent evil, makes possible an individual prophylactic and public health approach to treatment.

FACTORS IN TREATMENT

Prophylaxis

Prophylaxis has been emphasized as the ultimate in therapeutic measures. The prevention of communicable diseases by immunologic and public health measures directed against contagion and the communication of disease is generally accepted as a fundamental medical concept. Occasionally some special groups or individuals resist actions required by law for the prevention of disease. The physician does not take a permissive attitude toward such people but expresses his judgment as to the required course of action in the best interests of all. Failure of anyone to comply may then be followed by more vigorous attempts at education, and a concern for the cause of such attitudes in resistant persons.

Ignorance about rules for healthful living is less common today than ever before, but education in hygiene is a continuous responsibility of the medical profession. Blood testing is now a common legal requirement for marriage , and advice about sexual and venereal disease is given to young men and women. Premarital advice also may be sought by the engaged couple. Valid information about sexual behavior, pregnancy, lactation, and child care act as preventive measures against both physical and psychologic illness and disability. Teaching the habits of health is part of the physician's work in his role as an advocate of public health and as a therapist whose treatment begins with prevention. Incidentally, physicians themselves do not follow standard medical advice with regard to the yearly physical examination. The doctor, as a patient, may well need from other doctors the advice he intellectually offers to his own patients.

The patient's expectations

Most treatment processes are conducted in a two-person social system, *i.e.*, the doctor-patient relationship. The others who enter this field of interaction—intern, resident, nurse, spouse, parent, sibling, friend—are usually subordinate actors on the stage of the patient-physician transaction. Most workers in the field of medicine are well aware of the "quid pro quo" attitude which the patient manifests about arrangements for medical care. He accepts the idea of expressing himself rather freely about physical sensations, but is reserved and suspicious about his personal troubles or difficulties with others. In turn, after proper assimilation and coding of the data, he expects some action by the physician directed at alleviation of the symptoms or troubles. Awareness of the patient's expectations is frequently expressed in medical circles by such statements as:

"You have to do something for the patient"; "You have to give him something"; "The patient has a right to an ECG." However, there is insufficient awareness that the process of giving need not be in the form of a prescription, a laboratory examination, a special manipulation, or some magic formula for recovery. Many physicians are surprised to find that the patient considers adequate value to have been received as a result of the doctor's attentive listening, understanding, and the offering of another appointment to discuss the problems in greater detail. Obviously there is need for a great deal of re-orientation about what the patient considers "value received." A patient suffering from a severe migraine, even though convinced that important elements of his problem are emotionally induced, may be far from satisfied with a promise of further study and exploration; he expects immediate or early relief. Yet it is worth emphasizing that he may regard a sympathetic and understanding attitude in a doctor who is willing to listen, as an adequate return for his fee. Behind this provisional acceptance of the passive (listening) attitude of the therapist is an expectation that some process will ensue that will provide help. The physician can put to good use this expectation of being healed which the dependent person displays, based on satisfaction of his needs in earlier comparable situations. A child undergoes the experience that the laying on of a hand, a caress, a supporting arm around the shoulder, an attentive and sympathetic ear, or a kiss, takes the hurt away or at least diminishes the pain. These healing responses are attributed by the child to the magical powers of his parents. The doctor is looked upon by the patient as a helpful parent and as such is considered a possible source of comforting attention. The responses of approval, protection and attention are sought as substitutes for the love and affection expected from parents. Threats, punishment and disapproval are also parental reactions which the patient may anticipate from the physician. By being a "good patient" he diminishes the risk of punishment or disapproval and enhances the probability of becoming well. Use by the physician, however, of this type of relationship carries with it the implication that a more mature and more responsibly adequate relationship cannot be established. The patient's expectations are influenced by the nature of the immediate illness, the current problems in living, the level of sophistication, the family and social values, the total personality of the patient and the personality of the physician.

The physician's personality

The personality of the physician is an integral factor in the effects produced by all his treatment devices, whether additive, subtractive or manipulative. *The flexibility* of the physician is an essential quality in the management of the patient. As indicated by Hollender (13), the physician may have to treat a patient in diabetic coma in terms of a passivity-activity model. As the patient emerges from coma, the guidance-cooperation model is preferable; and when he is about to go home, the treatment pattern may well be one of mutual participation. The physician whose method of treatment remains fixed in one of these patterns, with no change in roles throughout the spectrum of patient-physician

relationships, may find his patient slow to recover and critical of the medical care received.

Rigidity and an unyielding nature, a preference for dealing with the patient on an intellectual level as though he were a physiologic object, and the avoidance of involvement in the patient's emotional problems are qualities in the physician which significantly influence treatment—too often unfavorably.

Identification with the patient affects some physicians. Renneker (14) in studies of patients with breast cancer found that the attending physician is often stirred deeply through identification with the dying patient. The desire not to be reminded of a previous traumatic experience may prevent an attitude of empathy which would be helpful in management. The undesirability of positive identification, as if the patient were a close personal friend or an intimate associate, has been sufficiently stressed.

Authoritarianism is a part of every doctor-patient relationship. The patient often needs and expects a certain degree of such control. Realistically, this should vary with the degree to which the physician's special knowledge makes it desirable that he make such decisions for the patient. The patient does not generally have access to this knowledge. However, too many patients have strong feelings of passivity and dependency which drive them to extract a maximal degree of authoritarian control from the physician, and to avoid taking responsibility for self-management and self-control even when they have the necessary knowledge. They will react with anxiety and undesirable behavior if their needs are not recognized.

Obsequiousness on the part of the physician toward persons supposedly in a prestige relationship to him may prevent development of the kind of doctor-patient relationship needed for therapeutic effectiveness. It creates a situation in which the patient determines the therapeutic procedure.

When *passive, dependent traits* are manifested by the physician, an atmosphere of doubt is created about the wisdom of his therapeutic procedures. Some patients with anxiety about retaliatory aggressiveness may, however, respond to treatment administered by the more passive type of physician with greater comfort.

The foregoing factors are but a few of the many personality traits which have significance for the physician in the management of his patients.

The quest for certainty

This universal human goal has a special poignancy in medical practice. It is present in the patient seeking help, whether for a threatening physical disorder or an emotional upheaval; he brings to the treatment situation certain basic desires which Masserman (15) has described as essential defenses. In essence, the patient's defenses are: 1) a feeling of indestructibility; 2) a belief that others are interested in him, even to the point of personal sacrifice; and 3) faith in some force or power, omnipotent and all-knowing, which in some way will protect him against danger. The physician a is representative of some significant figure from past experience. These essential defenses are utilized by the patient to find the

required qualities in the physician. Awareness of the patient's needs for such defenses to help fortify him against anxiety and fear, should be part of every therapeutic procedure.

Parallel with the patient's quest for certainty is the physician's comparable quest. Schwartz and Wolf (16) expressed it as follows: "It may be useful in exploring the problems and treatment possibility for each patient to think in terms of certainty and uncertainty, or of realistic and unrealistic efforts to achieve certainty and how this concept plays a role in effecting therapeutic results. Our system of education seems to give the impression that for every question there is a single definite answer. Every patient likewise hopes for a single, simple, definitive cure. This is unfortunate because the problems encountered in later life and their solution generally cannot be answered quite so definitely."

Masserman (17), in discussing the history of psychotherapy, described the skeptics Aristippus and Pyrrho as being doubtful of man's ability to perceive the real world. The senses by which man perceives properties are known to be deceptive; they vary in validity according to needs, preferences, emotions, and state of health. The perceptions are also altered by the morals and culture of the time, and the symbolic values with which the object is endowed. The quest for certainty is the quest for an illusion.

The patient's quest for certainty and his need for someone to help him even at a personal sacrifice, distorts the image of the physician as a person when perception by a patient is being experienced in pain, distress, anxiety or fear.

Transference attitudes and feelings

Transference is the term most commonly used to described distortion of the doctor-patient relationship in psychotherapy (18–22). Rapport, confidence, acceptance, empathy, relationships, and many other terms are used to symbolize that interpersonal reaction which characterizes the contractual involvements of treatment. These phenomena are seen and can be studied as elements in any system in which one person seeks help and another offers help. The term "transference" has been used most frequently to designate the special nature of the relationship in psychoanalytic therapy. Treatment of a patient has begun the moment he has decided to seek the help of another person. The acceptance by one person of a need for help from another is at the root of all medical practice. It encompasses the establishment of a relationship of dependency and the revival of the earlier attitudes experienced as a child when continuous protection, care, help and nourishment as a dependent were needed to maintain life and enable growth. In treatment, many of the patient's perceptions of the person caring for him express this need to see in the therapist the protecting or neglecting, the caring or the injuring roles of significant figures in his past. The response to the therapist may resemble that given to a father, mother, brother, sister, uncle, aunt, teacher, or best friend. This repetitive tendency throughout life is an extension of the principle involved in the behavior of any organism—repetition of the adaptive patterns which earlier have been operationally successful. When a person is frustrated, this repetitive tendency

becomes operative, even when extreme blocking of gratification occurs. The phenomenon of transference is part of the design of the various types of doctor-patient relationship previously described.

Infants and children endow parents with God-like magical powers when they are frightened, in pain or distress, or in any way insecure, and they find that parental intervention restores them to comfort and joy. These same attitudes, expectations and powers are transferred by the patient in adult life to his transactions with the physician. Although such reactions are a necessary psychologic aspect of the patient's healing process, unfortunately physicians may accept at face value what the patient believes about him, especially as it implies omniscience and omnipotence. Transference attitudes and feelings include:

1. *Dependency needs*, mobilized by stress of any kind, may be expressed realistically as a dependence appropriate to the disability, with recognition of the probable limits of a competent physician's ability to help. At the opposite extreme, these needs may be expressed unrealistically even to the extent of creating the expectation that the physician will give up his own interests in selfless devotion and accomplish for the patient what is beyond currently known medical science. The patient literally may want to remain in bed with all his needs cared for, even to being fed and having bowel and bladder functions looked after by others. Dependency cravings may be relatively minor or even ceremoniously proper at first, like enjoying breakfast in bed on Mother's Day, but may be encouraged to merge into the acceptable social role of illness which ultimately may reach a stage of regression that is malignant and nonreversible.

2. *Denial of dependency* by the patient is a defensive bravado, an ignoring of his anxiety. Such a defense may suddenly collapse into a state of acute panic or severe regression, to the surprise of all who accepted the defense at face value. The sick person, weakened by illness, harried by anxiety and beset with other problems in the family, may respond with combinations of the feelings and attitudes we have described.

3. *Feelings of anger*, *resentment*, and open hostility may be mobilized by unrealistic expectations. The patient may see himself as being treated with less consideration or thoroughness than others, or even negligently and incompetently to the degree of malpractice. In fact his feelings and attitudes may simply be a reaction to the physician's inability to satisfy an unrealistic, undetected expectation. Thus he may use the doctor-patient relationship to fortify a feeling of basic distrust about any interest or attention shown to him.

4. *Feelings of guilt* may be manifestations of the patient's hostile and aggressive intentions, or of his interpretation of his illness as a hostile or depriving act directed against friends or members of his family.

5. *Erotic feelings and shame* may be aroused by undressing. Examinations and expressions of interest by the physician, especially with regard to the erogenous zones, may be interpreted as having an erotic motivation, and may arouse an erotic response of reactive feelings of anger and shame with accompanying physiologic and behavioral changes.

6. *Feelings of envy and jealousy* occasionally interfere with the realistic doctor-

patient relationship. The patient feels that others may be getting better treatment.

The patient tends to see the many possible therapeutic interventions by the physician as powerful, magical controls which are used to help him. The doctor's willingness to intervene is an expression not only of healing power, but also of interest, protection and love. More latent are concerns about a possible malevolent use of these powers as expressions of anger and hate. The patient's perception of the doctor's office, the waiting room and other elements of his first introduction to the healer is colored according to such needs. If the office is unusually crowded, the doctor becomes endowed with powerful magic; people must seek his help in such large numbers because he is so effective. If the patients are few, then it is implied that much time is consumed in each one's care, and the doctor must limit his practice and show an unusual interest in each patient he admits. Each item in the office is used by the patient in this variable fashion to document what he wishes to believe about the doctor. In a positive orientation, the diplomas on the wall show the physician's effective training; no diploma is a manifestation of the humility of this great man. An ornate office is proof of success and ability; simple furniture shows that the doctor needs no special trappings to enhance his stature.

THE PHYSICIAN

Attitude toward the patient

Emphasis on a knowledge of self, so important in the treatment of patients with emotional illness, applies the treatment of all patients. The physician needs to face maturely any strong feelings of like or distaste for his patient. Gerty (22) said of the physician, "In his devotion to his calling, every good physician may have to combat at times disliking the things he has to do. He must not dislike humanity, and must have some measure of charity and tolerance for its foibles, weaknesses, and prejudices." Our previous experiences contribute to the attitudes we develop toward our patients. Significant among all these are the conditioning experiences of our medical education. Stoller and Geerstma (23), in a study of student attitudes, found that medical students prefer to view even the emotionally ill person from the point of view of organic pathology. Anxiety mounts as they have closer contact and responsibility for emotionally ill patients. This helps create the attitude that an organically ill patient is a desirable one, as compared to the undesirable anxiety-ridden or "uncooperative" emotionally ill person. The physician, whether he be internist, surgeon, pediatrician or psychiatrist, has the responsibility of learning about such personal attitudes, predilections or prejudices (positive or negative) toward patients and illnesses. In this way personal and professional judgments may come closer to being harmonized for the welfare of the patient.

Countertransference

Countertransference is the physician's reaction to the patient with feelings and attitudes similar to those he has manifested toward significant persons in

his past (24). Patient-physician relationships in which the reactions to the patient are realistic are complicated by the emotional need of the physician to repeat such feelings. These are counterparts, in the physician, of the patient's transference feelings. Responses to patients which are expressions of countertransference are therefore not based upon the reality of the situation. Such attitudes contaminate treatment. Guilt feelings may lead to treatment that does not go as far as it should. An attitude of reserve may prevent adequate examination of the patient. Strong feelings of superiority may mobilize attitudes and feelings which have been described as "the God complex" by several authors (25–26).

Countertransference feelings are to be distinguished from those which are reasonable, realistic, and appropriate to the circumstances. A patient may be excessively demanding, rude, and improper in his speech, manner and dress, or in other ways behave unacceptably and offensively. The physician, as a human being, is expected to react to such behavior with an attitude of taboo and nonacceptance. On the other hand, the physician's function in society realistically requires that he manifest a tolerant non-condemning reaction and an awareness that deviant behavior may be an illness. The degree to which he can be objective, and react with understanding rather than with anger, impulsiveness, and retaliatory or overtly aggressive behavior is a measure of the physician's awareness of his role in society and the maturity of his relationship to patients. The patient's positive feelings of dependence, confidence, security, affection, and overt intimate display may also arouse erotic feelings. Utilization of this rapport by the physician for unfair exploitation of the patient is not ethical, moral nor professionally rewarding. It may be understandable that the patient see the physician as a priest, a deity, or an Adonis, but it is indeed an error in judgment for the physician to accept these attitudes as realistic.

In discussing countertransference as a phenomenon of psychotherapeutic work, Heinman (27) indicated that emotional reactions of love, hate, helplessness or anger impel toward action rather than contemplation. They tend to blur the capacity of the therapist to observe and weigh evidence correctly. Treatment for the patient will be most effective when contemplation is not blurred by affective reactions.

THE INITIAL HISTORY AND THE TOOLS OF EXAMINATION AND TREATMENT

Initial history-taking

The first action in the treatment program is taking the initial history. It immediately gives the patient an opportunity to unburden himself about his anxieties. He tells what hurts him, his symptoms, and how they developed; in so doing, he has in a sense unloaded the responsibility for care and protection upon the physician. The very taking of the history has this psychotherapeutic implication on the part of the patient: "I have told you and now you will cure me; reassure me, or approve of how I acted." History-taking provides an opportunity for confession and the emotional discharge which becomes a constructive experience when it encounters an appropriate response. The physician's social

rule of neutrality prevents the patient from feeling too strongly rejected or guilty about what he expresses.

In the initial history taking and the subsequent contact with the patient there is considerable opportunity for offering suggestions or creating an atmosphere which decreases the patient's anxiety and feelings of insecurity. The author has pointed out (28, 29) that an effective history can frequently be obtained by indirect questioning. This avoids creating an atmosphere in which the patient assumes that because the physician asks questions about certain symptoms, he must have experienced them. This important basic rule concerning treatment cannot be overemphasized, if the frequent reports of iatrogenic illnesses are any indication of the extent to which suggestive history-taking influences the patient toward development of symptoms which later become problems.

The tools of examination and treatment

Rituals, mystic practices, and the use of symbols as special curative agents are more allied to the priestly portion of the priest-physician role (30). The physician recognizes that diplomas, certificates and licenses are special evidences of skills to many patients. The stethoscope, ophthalmoscope, otoscope and fluoroscope, to mention a few instruments, may symbolize to the patient the depth and intensity of the doctor's interest in him as well as his magical or God-inspired skills and avenues of contact and understanding. It is easy for the patient to shift awareness of the use of these tools to secure information into anticipation of their magically-endowed use to obtain the wished-for cure.

Many of the patient's everyday experiences suggest a causal relationship which fortifies his expectations. The farmer examines his soil and then adds a specific fertilizer; the deficiency is corrected. The attendant tests radiator water, adds a quart of antifreeze, and there is no further radiator trouble at low temperatures. Such experiences help the patient to quiet any doubts he may have about the God-like qualities of the doctor. He can fall back securely on the supposed omnipotence of the machines used by the therapist. The fluoroscope, the electrocardiograph, and the electroencephalograph have "cured" symptoms for every physician. The patient with severe precordial pain finds it reduced as if by magic after an ECG test.

The prescription blank also has an important psychologic meaning for patients. Its significance may be compared to that of the ritualistic words and acts and the powerful symbols and taboos which are standard curative practice in primitive medicine. The prescription is not to be depreciated with casual indifference as a scrap of paper transmitting authority to issue certain ingredients which on their own merits, will help the patient. The prescription also heals by magical persuasion. It can represent a gift from one who is powerful to help. It may possess all the potency of a primitive ritual which is perceived to have power to drive away evil and illness. It therefore represents more than the contents of a bottle or capsule, or the favorable mechanical alteration of the patient's physiology or biochemistry. That which is scientific in treatment, physiologically speaking, may be blurred by the magical, mystical and ritualistic elements with

which the treatment is administered. It is not to be wondered that many patients feel better within hours after the beginning of x-ray treatment for carcinoma.

There is a negative aspect to all of the factors that have been described in positive terms. Patients also express negative feelings about all these items. They find fault with impeccable offices and with competent examinations. The tools, it is claimed, have done damage during the examination. An unfavorable response to drugs may lead to suits for attempted poisoning through the medium of prescriptions which are sent to a fellow conspirator—the pharmacist. The patient is again reacting on the assumption that he is being treated in a manner similar to that which he experienced earlier in life. He had good reason to distrust the character and motives of his parents as they cared for him. How can he therefore think better of persons who, later in life, represent authoritative figures?

In essence, many of the activities, tools and rituals of treatment are based on concepts which relate illness to black magic and demons. Therapeutic measures stem from special qualities which allow God-like influences of a favorable nature to be transmitted to the patient. Knowledge of these magical, mystic, ritual and religious influences on the responses of the patient in the doctor-patient relationship is necessary in order to sharpen the physician's awareness of such factors and to use them appropriately in the evaluation of the patient, the application of therapy and the understanding of the results.

PSYCHOTHERAPEUTICS

Defense reactions

Denial of illness complicates the history, diagnosis and treatment (31). Many patterns of defense are utilized by the patient to deal with anxiety and fear, or to avoid awareness of any catastrophic or seemingly catastrophic situation. The patient may repress these reactions so he may not be consciously aware of what is happening. He may purposely suppress all such thoughts and assume that all will be rectified by refusing to see, dwell on, or talk about his troubles. Dependency to an extremely pathologic degree may occur; the patient seems to think that, by being childlike, he can turn over all his problems to the physician and no longer deal with them. Familiar maneuvers are the display of previously effective patterns of defense, such as compulsive cleanliness or busyness; intellectual conversation with the physician about illness as a participant-observer rather than as a patient; and the projection of anxiety and fear onto parents or a spouse who may collapse when told the truth. They represent methods used to deny anxiety, guilt, shame, disgust and fear. The method of dealing with illness will vary with the patient's personality, the nature of the problem needing solution, and the kind of patient-doctor relationship being established. Treatment includes an awareness of the psychologic defenses used by the patient, how to avoid destroying them, which ones to fortify, and which ones to utilize in such a way as to foster the aims of treatment for the patient.

Regression

Regression is a phenomenon observed in most treatment relationships and is used extensively as a concept in psychiatric medical practice (32). It is a useful concept for the management of patients under any kind of medical care. The patient seeking medical care usually has done so because of symptoms. Physically disturbing sensations and anxiety are the prime reasons for bringing the patient to the physician. Every disturbing experience motivates the patient to seek a solution to the problem which confronts him. The tendency to seek solution in patterns of reaction previously found to be effective is a corollary of the principles involved in concepts of homeostasis. Regressive patterns of behavior are characterized by a return to earlier ways of solving a problem, a tendency to respond with wish-fulfilling or impulse-ridden desires, and a decrease in the ability to put off desires for immediate gratification. The person becomes more introspective and preoccupied with himself, and interest in the external world becomes correspondingly narrowed. Often regressive phenomena have a direct relation to the severity and duration of illness. Severe regression may take place in the dependent, insecure personality, to an extent altogether out of proportion to the degree of physical suffering. Personality patterns in which overcompensated independence is a facade for marked feelings of insecurity may, under stress situations, be followed by a malignant type of regression.

Regressive phenomena alter the manner in which the patient comes for treatment, and they influence the physician's treatment procedure. They may create problems in management of the patient, for example, when even a reasonable degree of regression leads to criticism and reproach by the physician. A too-ready response by indulging the symptoms and behavior of regression may retard recovery and complicate the doctor-patient relationship. Malignant regressive tendencies which develop into states of complete helplessness can thus be induced in the patient. The increased demands of the sick person may arouse intense feelings of hostility and rejection in the physician. The patient may respond to such reactions with the only weapon he may possess for retaliation—deeper regression. Death may ensue from a malignant regression manifesting itself by refusal to eat, apathy, incontinence, bed sores, and secondary infection.

Suggestion, relaxation, and hypnosis

These measures are used too frequently as the only form of treatment. Some forms of suggestive intervention take place in the treatment process. Germane to the impressive influence of these factors in treatment (33–35) are: the patient's great need for help when in pain or under stress; acceptance of a physician as qualified to relieve and to help; the development of a significant interpersonal relationship between the physician and the patient (the greater the stress, the greater the need for the guidance-cooperation model); and the qualities of the person treating the patient (the greater the need for authoritarian control, the greater the need for using methods of treatment involving suggestion). In the preceding sections of this paper, the significance of suggestion in the treatment of the patient has constantly been re-emphasized.

Responses to suggestive influences are based upon an uncritical acceptance of what is said or implied by another person. The degree to which uncritical acceptance is a personality trait of the patient has an important bearing on the degree to which suggestive influences operate. There is a continuum from no response or only a slight influence at one end of a scale, to complete hypnotic control of the patient at the opposite end of the scale. "Relaxation therapy" has a degree of suggestive influence which may approximate that of hypnosis. The long period of maturation in the growth of the individual permits the development of deeply ingrained inclinations toward passivity, dependency and regression. When subjected to suggestion, relaxation therapy, or hypnosis, such patterns of regression are mobilized in association with appropriate body chemical changes and motor, sensory and autonomic nervous system reactions. The most productive utilization of such therapy comes with an effective understanding of personality development, of psychodynamic principles, and the nature of transference phenomena. Without such understanding, influences will be created and controlled only as long as the patient accepts an activity-passivity type of relationship in treatment.

Spontaneous recovery

Treatment is generally conceived as encompassing some kind of action, whether it be additive, subtractive, or manipulative. The significance of nonactivity as treatment is not generally recognized. In the foregoing discussions, the psychotherapeutic effect on the patient of a passive, permissive, receptive non-condemning attitude has been pointed out. The patient perceives the therapist as waiting for the proper moment. After the therapist has learned all the facts, the patient believes that he will eventually "cure" or remove the symptoms or discomfort. During this waiting period the patient may recover. The phrase "skillful neglect" has been used to describe the non-active management of a patient who has a self-limited condition from which he is expected to recover within a short time, or an illness for which known therapeutic measures are ineffective. As Hyman (36) has said: "The intelligent doctor humbly recognizes the healing art of nature. He learns to avoid interference with the favorable course of the disease." Many patients will respond with considerable relief to the prognostic expressions of the physician and accept the advice that no specific treatment in the way of drugs or manipulations is necessary. Other patients are unable to accept a passive non-giving attitude and feel threatened by what they consider gross neglect or aloof indifference; they may provoke the physician into therapeutic procedures unwarranted by any demonstrated helpful potential. Exploration of the patient's emotional attitude to his illness, deeper understanding of his total life situation, clarification of his subjective emotional states through return visits, or even major psychotherapy, may be necessary. Some patients utilize the situation to claim that their disrespect and depreciatory attitudes toward the physician are warranted. The fact that nature will heal, however, does not justify a physician's neglect, irritation and anger, misunderstanding of the person, depreciation of the illness and symptoms, or failure to relieve discomfort.

Factors underlying procrastination

Procrastination in seeking medical attention involves a complex interrelationship of factors, including denial of illness. Among the causes for procrastination mentioned in the literature (37–41) are:

1. Socio-economic factors, more frequently involving attitudes toward money than actual lack of resources. Shame over accepting free care may be significant.
2. Social status and cultural attitudes toward medical care influence the acceptance of treatment. Certain symptoms may be passed over lightly in one social group but viewed with great alarm in another. The social definition of many signs and symptoms and of the doctor's role may drop an iron curtain between the doctor and the patient.
3. Fear and anticipation of pain may induce a negative reaction toward seeking help.
4. Illness may be seen as weakness or inferiority. Status is maintained by avoiding medical care.
5. Shame about genital parts, nudity, and certain internal organs may engender reserve about physical examinations.
6. Depressed persons often may regard themselves as worthless and not deserving medical care.

Awareness by the patient of narcissistic and exhibitionistic desires in connection with receiving medical care may lead to avoidance. Such an avoidance may be in line with a general taboo against being looked at—the risk of being admired.

THERAPEUTIC ACTIONS

Action follows upon the determination of therapeutic goals. A plan is put into effect. Menninger (42) described such action as *subtractive* (*e.g.*, the removal of a tumor), *additive* (*e.g.*, administration of medicine or immunizing agents), and *manipulative* (*e.g.*, massage or splinting). Many patients are the recipients of two or all three types of action. The physician who views his role as an interacting one with the patient, will find himself evaluating a number of variables—the kind of preparation necessary for his therapeutic actions, the patient's expected and actual reactions to the situation (or field) in which treatment is taking place, and his own aspirations and reactions. A trial prediction of the outcome of this interaction should be forming in the mind of the physician and later related to the actual outcome, in order to determine future treatment. Each bit of action directed at treatment can thus be seen as stemming from an hypothesis. Results of the continued search for evidence regarding the patient's response will verify or alter the hypothesis. A more detailed discussion of methods is reserved for another paper.

Therapeutic actions, according to Hyman (36) include the following:

1. Giving advice regarding such factors as diet, hygiene, climate and prophylaxis; and using psychotherapy.
2. Conducting or ordering manipulations having therapeutic value, for example, artificial respiration.
3. Using instruments for procedures such as dilatation, irrigation, inhalation, douching and spraying.

4. Giving medicaments or fluid, either by mouth or parenterally.
5. Applying physical therapy.

These actions are based upon such concepts as helping the body to overcome noxious influences, restoration of chemical imbalances, correction of physiologic disturbances, immobilization or resting of parts to facilitate the processes of restoration, and stimulation of physiologic processes spontaneously operative in the direction of healing.

Rest

Early ambulation after an acute illness, childbirth, surgery, or during a chronic illness has been developed as a therapeutic action, displacing the earlier procedure which emphasized complete bed care. Rest as a factor in treatment also has its advocates. Like exercise, it may be prescribed with cultist enthusiasm. Its application may be best understood under the following headings:

1. Bed rest is used most commonly as a technique of total immobilization. The concept of partial immobilization for treatment of a fracture or an arthritic part seldom encounters disapproval. The rules for total or partial immobilization are usually explainable on physiologic grounds and are generally well understood. There is, however, some danger of unnecessary immobilization, carried out to satisfy the physician's frustration in the face of a patient's insistence that "something be done."

2. Rest as a consequence of advice to "take it easy, relax, take a vaction" nay end with the patient becoming worse for the experience. A person who engages in constant motor activity to ward off awareness of alarming feelings, thoughts and motor tensions may find a leisurely vacation a restless experience. The depressed or anxious patient needs psychiatric evaluation before being advised to take a "therapeutic" vacation. Rarely does the change constitute an effective therapeutic measure. The physician, for the length of the vacation period, is relieved of his own troubles in dealing with such a patient, but he often loses the patient to another physician after the return home, because of the patient's feeling of not being understood.

3. Vacation as a form of environmental manipulation to separate a person from a vicious cycle of interactions with other individuals may be very successful if other problems are not stirred up in the process. The vacation may enable the patient to find solutions to his problems when he is not involved in a vicious cycle of anxiety-provoking circumstances. The advice to "take a rest" is a prescription which often requires more thought than it receives. Rest is at one end of a scale of therapeutic procedures ranging from self-healing to the extremely active interventions involved in surgery.

Surgery

Surgical procedures are common subtractive, manipulative, and additive actions in therapeutic management. Much thought should be given to the meaning of surgery for the patient.

Surgery and the need for self-punishment. Surgery is a stress situation. Less easily perceived is the patient's subtle need to experience trauma and pain. The

patient who seeks or welcomes such a painful situation is actually making some attempt at an adaptive course of action which, to him, has positive meaning. The painful situation may be used to avoid an even worse experience, or as a means of obtaining some unusual gratification. As Menninger (43) has indicated, the painful surgical condition may be accepted as a procedure whereby the patient avoids some serious mental disintegration. A surgical operation and painful situation may also be welcomed as: 1) a punishment whereby the patient atones for real or fancied sins; 2) a procedure for diminishing guilt feelings over forbidden or unsanctioned thoughts, strivings or acts; and 3) a compromise whereby the sacrificial offering of a less important part of the body guarantees the safety symbolically either of the whole, or of an organ of greater significance. Distressing life situations are avoided by patients through hospitalization. Such avoidance of anxiety may be associated with symptoms suggestive of an acute abdominal illness over so long a period of time that finally a surgical intervention becomes necessary. Rarely does the patient seeking to solve a personal problem by a painful experience succeed in doing so; he usually fails to establish the desired psychologic balance. The post-surgical course then becomes exceedingly stormy, sometimes after a brief initial period of what seemed an unusually satisfactory recovery from the operation.

Witt and Cheavens (44) point out that surgery and psychotherapy should not be confused. The former does not substitute for the latter. An operation, contrary to popular lay opinion, can never function as good psychotherapy; if performed in order to satisfy some need of the patient, in the absence of objective surgical indications, it is more than unnecessary—it may be dangerous. Recognition of a psychic disturbance before surgery is performed, and recognition that the alteration in physiology will not alter the psyche, can prevent an undue amount of suffering for the patient, the family, and the surgeon.

Sometimes the astonishing idea is expressed that, although there are no abnormal physical findings an exploration is justified, or that a certain operation is of value because it will have positive psychologic import for the patient. It may be true that in some instances surgery performed for its psychologic influence does seem to bring about a restoration of psychologic equilibrium. At best, however, this can be only a temporary phenomenon. Such a positive result can be predicted only accidentally. This approach can, under no circumstances, be advised as a reasonable and logical course of action in the best interests of the patient; it is not even within the lowest limits of sound medical practice.

Body alterations. Requests for alterations in the body are frequent, and are often distressing for the surgeon. The patient anticipates a result that involves a change in personality, the achievement of certain aspirations, and improved success in living. These hopes have no better basis in fact than can be substantiated by advertising, or induced by the propaganda power of our mass communication media. Clothes are presumed to make the man. Napoleon's small stature is popularly accepted as the origin of his drive to greatness, based on his reaction to the induced feelings of inferiority. Elevator heels become necessary equipment

for success in love and work for the small man. Plastic surgery has similarly raised the widespread but unfounded hope that an alteration in the design of a nose, the removal of a facial blemish, or the surgical modification of a bosom will bring enhanced success in love, work and social status. Barker (45) and others have pointed out the tendency to overestimate the potential bad psychologic influence of a physical disability. The power to effect improvement in a person's total life situation by an improvement in physiology alone has likewise been overrated. Before the decision is made to alter the body contour surgically, it is pertinent to investigate the motivation, sources of anxiety, and nature of the problem to be solved by this act. MacGregor, Hill and Silver (46) have convincingly shown the urgency of understanding psycho-social factors in evaluating the request and in reaching a responsible decision to proceed with the correction of a facial deformity. In the study of a continuous series of patients requesting such plastic surgery, and having no other complaints, the conclusion was clear that the desire to alter even an obvious facial deformity has significant neurotic motivation and may best be regarded as a symptom of neurosis. In the absence of a plan which includes psychologic and socio-cultural aspects, the abrupt removal of a defensive system (which the deformity has often become) may result in so many new problems of readjustment as to generate overwhelming anxiety and precipitate a neurosis or a psychosis. Less malignant, but more troublesome to the physician, may be paranoid litigious attacks after the operation, when the patient finds his aspirations unsatisfied.

Mutilation, removal of defenses, and deformity. Palmer and Blanton (47) and others observed that certain organs have, in addition to their real functional importance, a massive unconscious symbolic significance for the patient. Surgical procedures on any organ so endowed may be regarded as highly dangerous and potentially deforming, disfiguring or castrating. The nose has been symbolically equated with virility; beautiful legs with being wanted and admired by men; a well-developed chest with masculinity; and a well-developed bosom with the role of siren or mother. Each organ has its own special significance for the patient, and is related to an ideal image in appearance and structure. Any surgical procedure with the potentiality for deformation irrespective of the potentiality for maintaining life and well being, can precipitate a psychoneurotic or psychotic breakdown by threatening the special symbolic power of the organ affected. Consideration of this factor in surgical planning may lead to a more favorable outcome. Mammectomy is probably the most common of all amputations of external parts. When the breast has been especially effective as a beautifying, attention-getting, or response-eliciting organ, a state of depression may follow closely upon its removal. Renneker and Cutler (14) have emphasized the importance of acquainting the breast cancer patient with the realistic facts concerning that disease, so that she is aware of the real danger to life and is impressed with the urgency of immediate action rather than dilatory tactics to maintain the integrity and usefulness of the breast. This avoids the risk of a mental disturbance or a negative attitude on the part of the patient even though the operation may have been successful.

Prolonged illness of any kind permits a patient to accept a dependent social role without any loss of status or accumulation of shame or guilt. The correction of tubercular lesions, cardiac surgery and many orthopedic procedures leave the patient prone to this attitude psychologically. Mitral commissurotomy and other cardiac operations have been evaluated for their psychologic effects. Fox *et al.* (48) investigated the adaptation to the prolonged dependency induced by a disabling terminal disease, as well as the reaction to imminent death. Kaplan (49) found the heart to be a focal point in the personality of the patient. Adaptation to a "weak" heart involves the development of a style of life in which satisfactions will be deeply threatened by any possibility of recovery from the illness. Prolonged illness creates not only acceptance of dependency, but also encourages aggressiveness toward authority ("I'm sick; they won't do anything bad to me."). The choosing of an occupation, the marital situation, and other sociocultural or recreational activities may not be as readily acceptable to a recovered patient. Illnesses involving repeated examinations or manipulation of the genital organs or erogenous zones may have prolonged effects on the defenses of rigidly moralistic persons.

Direct influences of surgery. Surgical situations obviously lead to stresses, and these must be viewed as possible precipitants of a neurosis or psychosis. The patient may be predisposed to the psychopathologic form of adaptation by his cumulative previous experiences which have led to the development of characteristic, pre-morbid patterns of perceiving, feeling, thinking and behaving. Precipitants of major psychic disturbances in association with surgery include: 1) resemblances to previous traumatic situations (experience with physicians, anesthesia, painful manipulations, post-surgical discomforts, or identification symbolically with earlier traumatic experiences at the hands of significant adults) which revive severe latent anxieties that combine with the current manifestations to arouse a hyperacute state of anxious distress; 2) a current life situation which encourages perception of the surgery and illness as a retaliation for improper behavior; or 3) the results of surgery on the brain, or of postoperative biochemical imbalance, which so affect the patient that he is unable to evaluate the external world accurately; awareness of this lack of capacity creates anxiety which exaggerates the inaccuracy of perception and sets up a vicious cycle with a potentially catastrophic termination.

Anesthesia may be a precipitant of acute anxiety; this stems from the fear of being overpowered and rendered helpless, of losing control and being in danger of suffocation, and thus becoming the defenseless victim of malevolent interests. Patients who cannot relax their control of internal impulses which they perceive as dangerous, or surrender their control over the thoughts and behavior of others which they view similarly, are particularly susceptible to panic under the induction of total anesthesia. In addition, there is always the risk of physiologic balance being seriously disturbed by an additional stress in the physical state; the precariously balanced patient with heart disease, liver disease or diabetes, or the acutely ill patient in severe pain, are examples. Thus physiologic disharmony can induce psychologic disturbances.

RELATION OF SYMPTOMS TO TREATMENT

Pathology versus symptomatology

The frequency with which organic pathologic lesions are found in persons past 50 years of age, and the significance of such ubiquity for diagnostic evaluation has been pointed out by the author (8). The diagnosis must be related to the temporal sequence of the organic pathologic changes and the subjective complaints. Failure to ascertain that the complaints long preceded the appearance of the organic lesions and are not congruent with the degree of abnormality currently observable, may lead to a course of treatment which is insufficiently relevant to the total range of the patient's need for help. The ease with which signs, symptoms and complaints can be related to observed abnormalities is reinforced by the possibilities of chance, and heightened by the high incidence of pathologic lesions in the older age group. For instance, complaints of pain in the extremities, weakness of the legs and difficulty in walking more than a short distance can be expressions of a long-standing phobic reaction. Symptoms of this type are frequently seen in older persons. Arteriosclerosis is so common, however, in this age group that the diagnostic conclusion is liable to be circulatory impairment of the extremities due to arteriosclerosis. The treatment is then directed exclusively toward alleviation of an impaired circulation, which may actually be impaired only to an insignificant degree. Because of the ever-increasing numbers of old people, there should be greater discrimination in relating pathology and symptomatology. Treatment should not be directed toward pathologic lesions that have not been identified.

Therapeutic externalization

Treatment that involves directing the patient's interests into external channels has received greatest emphasis in psychiatry under the name of occupational, recreational or vocational therapy. It is rapidly coming into use in the treatment of chronic disability. A greater awareness of the value of this externalization is also being shown in the treatment of patients in general hospitals. Regressive tendencies are thus decreased and the dangers of a ruminative preoccupation with illness becomes diminished in association with judicious use of these measures. Arts, crafts, sports, games, hobbies, music, recreations and even the informal social life of the ward or floor, in contrast to the isolation of a private room, may be used with therapeutic intent, and not simply as a means of diverting from the physician the irritations of a difficult patient.

Treatment of functional disorders

Functional disorders distress the physician by their failure to respond to treatment. Glover (50) described the problem as follows: "There is no doubt, however, that in whatever form psychological disorders may appear, whether as pure neurosis, or as psychological complications of organic illness, they provide the general practitioner with some of the most harassing of his therapeutic problems. No matter how exhaustively he may examine his patient, or

how sedulously he may apply different methods of organic treatment, the physician may find himself faced with a negative therapeutic reaction. To put it quite simply, the patient just refused to get well." Nevertheless, many patients with so-called functional disturbances respond favorably to a variety of chemical, physical and manipulative ministrations seemingly directed at organic illness.

Life situations, emotions, and therapeutic interventions are intricately interwoven. These patterns have been studied experimentally by Wolff (51). Favorable life experiences are associated with certain qualities of emotional response. These reactions are associated with autonomic and somatic nerve stimulations which alter vascularity, secretion, mobility, hormonal secretion, muscular irritability or motor response. Therapeutic measures, therefore, which do not also take into account the life situation and emotions may fail to achieve their goal, other things being equal. An ulcer patient continually involved in anger-inducing situations may fail to respond to alkali. A job situation, a marital problem, a neighborhood stress, may be constantly undoing the effects of agents which are known to heal ulceration. When a structural alteration is present, treatment may be along such lines as removing offending parts, encouraging drainage, protecting a part from traumatic influence, or changing the biologic balance in favor of healing through the use of chemicals, antibiotics, hormones, or biologic agents. These same measures may also favorably influence the patient with a psychophysiologic disturbance, a neurosis, or a psychosis. Such responses to physical, organic, and chemical therapies are often used as evidence to support an all-encompassing organic orientation, and unwarranted conclusions may be reached if based solely on the therapeutic response. It is imperative that the physician be aware of the magical, ritualistic and mystical elements in the patient's use of treatment and understand the phenomenon of transference as a factor in therapeutic results. The patient with a functional illness primarily needs treatment by psychologic means, with physiologic measures as secondary instruments to alleviate symptoms, create comfort, and tide over brief episodes or acute exacerbations. Therapy should be directed at as much improvement in maladaptive living and thinking as is consistent with the therapeutic measures available for use. The importance of the psychologic overlay in illnesses associated with pathologic physiology is creating a new interest in a comprehensive approach to the patient.

Gain from illness as a therapeutic deterrent

Secondary gain from illness has been recognized as a serious deterrent to beneficial results. Resistance to getting well seems a paradox, yet it is common phenomenon in medical practice. The illness which brings the patient to the physician may remove him from situations which have caused him much more unhappiness than any physical discomfort. To get well means a return to the old problems and a renewal of the conflict. A doctor-patient relationship that is too "good" may delay recovery. An illusion that the patient has now found a real savior—a person who can offer comfort, advice, security, love and affection—will make him reluctant to exchange a "good thing" (illness) for the uncertain

benefits to be derived from recovery and loss of the relationship. Feelings of hopelessness retard the patient's recovery rate. Lack of awareness by the physician of possible interference with progress because of the secondary gain motive may also seriously hamper or distort treatment. Early recognition of such interferences, and understanding of and neutralization of their effects on therapy are essential to the total treatment of the patient. Secondary gain through illness becomes a serious problem when the subtle need for traumatic experience induces lack of cooperation, accidents, the forgetting of instructions and finally surgical intervention.

Terms of payment

The patient sees himself in a contractual relationship in which, for "cure" or relief, he pays a fee. He may not be aware that he can also be paying a fee for services by which a cure, or relief, will not necessarily be obtained. The amount of the fee should be clarified as soon as possible, as well as how it is to be paid, when, and for what.

A danger inherent in the fee system is that therapeutic goals, the nature of the therapeutic actions, and the length of treatment become intimately involved with the ability to pay. Physicians who have an aversion for negotiating openly and professionally about the fee, may find themselves being taken advantage of for this attitude. This in turn may influence the physician to reduce his efforts and interest in behalf of the patient. The abuse of patients by undue charges or by unnecessary prolongation of treatment is strictly unethical. However, despite many statements by patients about such abuse, there is generally a greater degree of honesty in physician-patient monetary relationships than in any other two-person contracts of a professional nature.

Considerable controversy exists about fees and fee arrangements, but a discussion of them from the standpoint of medical economics is not germane to this paper. As a factor in treatment, however, the symbolic significance of money to the patient, his trust or distrust of the pecuniary interests of professional people, his attitude toward fees and his interpretation of the physician's economic well-being all contribute to the effectiveness of treatment in a complex, and all too often, a negative fashion.

Errors in treatment

A common idea about errors in treatment is that they are related to incorrect evaluation of etiology and to diagnostic inaccuracy. Four factors (57) are the source of most errors in treatment today: false authority, blind custom, ignorance, and a specious pretense of competence. The acceptance of certain drugs because some groups of patients have benefited from their use, is being subjected to greater scrutiny than heretofore in order to determine whether the influence of chance and other variables has been taken into account. Double-blind studies and the use of control groups to weigh the influence of attention, suggestion, persuasion, and reassurance produce evidence that seems to diminish the alleged effectiveness of many drugs and other agents of claimed miraculous powers.

Translation of the findings of uncontrolled studies into over-optimistic therapeutic proposals are deterrents to the effectiveness of treatment.

Length of treatment

Standard medical and surgical procedures are too often perceived as a single step—the classic "magic bullet"—by which the goal of "curing" or alleviating the symptom or bringing about maximal use of impaired parts is attained. The treatment is then ended. In psychotherapy, Freud (53) was concerned with the trend toward an interminable relationship with the patient. Certainly in psychoanalysis and psychotherapeutic work, the end-point of treatment is far from clear; as a re-educational process, once begun, it may continue without further interruption or with intermittent periods of resumption of treatment. In psychotherapy especially, there is need for reassessment of the secondary gains in treatment and of the reaction of patient to doctor and doctor to patient, as they affect the length of the treatment relationship. Recurrent symptoms may be mistaken for an exacerbation of the original difficulty which brought the patient to the physician; actually they may be attempts to extract more sympathy and pity from the doctor and the family. Dependent feelings, the need for a protective supportive person, and an erotization of the feelings for the doctor create the atmosphere for a prolongation of treatment beyond what is necessary for "recovery." In several studies dealing with chronicity of illness in medical clinics (54, 55) the author has emphasized the great influence of dependency needs in altering symptoms and complaints, and thus the diagnosis, treatment, and length of treatment. Countertransference, and attitudes of hostility created by equating the patient to disliked significant figures in the physician's past may lead to an undue abbreviation of the treatment relationship. A positive relationship to the patient based on re-enjoying vicariously some significant loved figure in the past may lead to a prolonged course of treatment as the physician clings to the patient.

CONCLUSIONS

Treatment is an attempt on the part of the physician to utilize his skills in the service of the patient seeking help. It is essential that he know the patient thoroughly before taking the designed therapeutic steps. This includes not only a knowledge of the physical make-up, but also the ambitions, values, morality, compulsive tendencies, obsessive preoccupations and as many facets as possible of the patient's life situation and personality development. Essential also is an understanding of the concepts used in biochemical treatment. In addition, it is important that the physician have a thorough knowledge of the patient's psychosocial background. The doctor-patient relationship is a special two-person social system with a variety of ways and means—physiologic, chemical and psychosocial—for helping the patient.

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Abstracts of Current Literature

COEXISTENT CHRONIC NONCONGESTIVE GLAUCOMA AND SENILE CATARACT: SURGICAL TREATMENT.

Bessiere, E., and Pelegris, G. *J. Internat. Coll. Surg.* **35:** 77 (Jan.) 1961.

When advanced cataract is present in an eye affected by chronic glaucoma, the best procedure, whenever feasible, is to intervene first against the glaucoma and then to extract the cataract. The choice is altered in the case of an elderly patient, and a combined operation for the two diseases should then be considered. The technic is described for such an operation. It incorporates extraction of the cataract with the procedure used by Legrand of sclerectomy with extraction of the lens. Total iridectomy and intracapsular extraction eliminate some of the risks of loss of vitreous humor, enclosure of the iris in the wound, reactions of the iris, and factors of obstruction of the fistula. The possibility of loss of the vitreous humor also is reduced by care in preoperative and intraoperatory preparation. When it seems likely to occur, extraction of the cataract is abandoned and sclerectomy alone performed. The after-effects of the combined operation described are usually those of simple cataract extraction. The functional results depend upon the evolutive stage of the glaucoma.

ADRENOCORTICAL HYPERFUNCTION IN ASSOCIATION WITH ANAPLASTIC CARCINOMA OF THE RESPIRATORY TRACT.

Bornstein, P.; Nolan, J. P., and Bernanke, D. *New England J. Med.* **264:** 363 (Feb. 23) 1961.

The first case of oat-cell carcinoma of the trachea in association with hyperadrenocorticism is reported. The patient had an unusually high plasma cortisol level and an increased endogenous rate of cortisol secretion. Both cortisol and corticosterone were found in increased quantities in the adrenal glands. Corticosterone may have been partly responsible for the severe electrolyte disturbances observed. Aldosterone was found in only very small quantities in both urine and adrenal glands. The literature concerning the association of anaplastic carcinomas of the respiratory tract with hyperadrenocorticism is reviewed. It is concluded that the respiratory-tract carcinoma antedates the adrenal hyperplasia and that the adrenal glands, not the tumors, account for the excessively high corticosteroid production. It is suggested that high levels of ACTH may be present in these patients, although the source of this ACTH, whether the pituitary gland or the tumor, and the precise manner in which the adrenal glands are stimulated, has not been established. (From authors' summary and conclusions.)

STUDIES ON FLUID AND ELECTROLYTE ALTERATIONS DURING TRANSURETHRAL PROSTATECTOMY: I.

Ceccarelli, F. E., and Mantell, L. K. *J. Urol.* **85:** 75 (Jan.) 1961.

An investigation of physiologic changes in patients undergoing transurethral resection showed the following: a quantitative decrease in the circulating plasma volume, a postoperative decrease in extracellular sodium concentration, a postoperative decrease in serum chloride concentration, an increase in weight, and an increase in hematocrit. From the presumed amount of water picked up and the decrease in the serum sodium level, an absolute loss of sodium from the body was postulated. The duration of surgery and the amount of tissue resected did not appear to affect the changes in serum chemistry determinations or body weight. Neither was there any correlation between the amount of irrigating solution used and the plasma volume, sodium level, or weight change. Hemolysis of red cells was

not observed in postoperative blood samples. The transurethral resection reaction syndrome was found to occur with the blood pressure varying in either direction or not at all. The majority of patients undergoing transurethral resection will adjust to the changes enumerated and have a benign course, but measures to prevent the reaction syndrome should consist of: a nonhemolytic irrigating solution under as little pressure as is consistent with resectoscopic vision, avoidance of exposure of the capsule with opening of venous sinuses at least until near the termination of the resection, and limiting the time of resection to no more than sixty minutes. Carefully administered hypertonic saline is the treatment of choice once the reaction syndrome is established.

LE FOIE CHEZ LES VIEILLARDS. (THE LIVER IN THE AGED).

De Grailly, R. *Rev. Hyg. Med. soc.* **8:** 41, 1960; through Excerpta med. (Geront. & Geriatrics) **4:** 128, 1961.

In 120 healthy subjects between the ages of 65 and almost 100 years, equally distributed between the two sexes, a study was made of the liver. With intervals of a few weeks to several months, general, functional, physical, and radiologic examinations were made, at least three times for each test person. The clinical examinations revealed only a paucity of general and functional symptoms. On measurement of the relative and absolute liver dullness, a decrease in volume appeared to be more frequent than a normal size or an increase in volume; sometimes, there was a change in form (bell-shape), and ptosis was also relatively frequent. Results of the radiologic study completely concorded with those of the physical examination by means of percussion and palpation. Of the liver function tests, galactose loading appeared to be disturbed in a high percentage of cases; it seems that this disturbance runs parallel to glycogen depletion in the liver. In 95 per cent of the women (men, 15 per cent), the coagulation time appeared to be lengthened, whereas the bleeding time was normal (due to exclusion of the ovarian function?). In biopsies, two lesions were distinguished: 1) general pathologic phenomena that occur both in adults and in the elderly, inter alia incipient cirrhosis, fatty degeneration; and 2) a specific anomaly of senility—arteriolitis obliterans. In addition, the glycogen depletion of the livers examined was considered to be a striking feature. From this study, the following conclusions are drawn with reference to the composition of the diet for elderly people: quantitatively sufficient calories, qualitatively many carbohydrates, a moderate but sufficient quantity of proteins, and no saturated fatty acids.

A NEW PARENTERAL ANTIDEPRESSANT (ELAVIL).

Dorfman, W. *Dis. Nerv. System* **22:** 145 (March) 1961.

Amitriptyline was given to 18 patients with depression accompanied by anxiety, both orally and parenterally along with electroshock therapy. Fourteen others received only the drug by these two routes. The parenteral dosage was 20 mg. intramuscularly in all cases. It was given immediately following the reaction from shock treatment when this kind of therapy was used. Amitriptyline usually was injected three times weekly but less frequently in elderly patients. Orally, the dosage was three to nine (25-mg.) tablets daily according to the patient's needs and tolerance. Parenteral administration was sometimes continued after an acute depression had been alleviated. Oral medication was continued at a dosage of one-half to six (25-mg.) tablets per day. A satisfactory response with recovery was achieved in 17 of the 18 patients during therapy with the drug in combination with electroshock therapy. Fewer shock treatments were required than during previous episodes of depression. An excellent result was obtained in 8 of the 14 patients with the drug alone; most of these had failed to respond to other treatment. In some patients, the drug facilitated psycho-

therapy. It is concluded that amitriptyline used parenterally aids the "total" treatment of many patients.

AGING FACE: SURGICAL MANAGEMENT.

Fomon, S.; Bell, J. W.; Schattner, A., and Syracuse, V. *Arch. Otolaryngol.* **73:** 153 (Feb.) 1961.

The management of the aging face presents two problems, *i.e.*, the removal of the redundant skin and the eradication of the wrinkling. This paper is devoted to management of the latter. The surgical anatomy of the mimetic muscles is discussed in a manner to show which ones can be dispensed with, with little physiologic disturbance, and which ones must be preserved if deformities more disfiguring than the wrinkles are not to ensue. The surgical technique for the eradication of the wrinkles is described in detail. The wrinkles are arbitrarily classified as of 1) the upper part of the face (glabella, forehead, eyebrows, and eyelids); 2) the middle part of the face (nasolabial and nasal); 3) the intermaxillary region; 4) the lower part of the face; and 5) the neck. (From authors' summary.)

USE OF DEXAMETHASONE IN TREATMENT OF CEREBRAL EDEMA ASSOCIATED WITH BRAIN TUMORS.

Galicich, J. H.; French, L. A., and Melby, J. C. *Journal-Lancet* **81:** 46 (Feb.) 1961.

Fourteen patients with increased intracranial pressure as a result of brain tumors were treated with dexamethasone to determine its effect on localized cerebral edema. Six patients were treated during their hospital stay, and 8 patients were treated before surgery. Two patients received 40 mg. of dexamethasone phosphate into the carotid artery at the time of angiography. The majority received 10 mg. intravenously initially, followed by 4 mg. intramuscularly every six hours until a maximal response was achieved. In patients undergoing surgery, this schedule was continued two to four days postoperatively. Dosage was then gradually reduced over five to seven days using the oral, free-alcohol form of the drug. Such therapy was continued for five weeks in some patients. Antacids were given to protect against a possible ulcerogenic effect, and anticholinergic agents were given after the maximal effect of dexamethasone had been obtained. Judged by relief of signs and symptoms of increased intracranial pressure, 13 of the 14 patients were benefited. Nausea, vomiting, and depression of the sensorium were the first symptoms to be completely alleviated. A neurologic deficit was alleviated in 8 patients. Improvement in neurologic function was related to the function and type of tumor, patients with metastatic tumors showing more improvement than those with glioblastomas, and these in turn showing more improvement than those with astrocytomas. A response was evident within twelve to eighteen hours, and maximal neurologic improvement usually occurred within a week. Continuing improvement sometimes was observed for as long as two weeks. In 5 of 11 patients who were hemiplegic or hemiparetic, motor function improved, and in 2 others there was improvement in the strength of the affected extremities. Improvement occurred in 4 of 5 patients with aphasia. Homonymous hemianopsia disappeared in 2 patients. Intractable temporal lobe seizures ceased in a patient so affected. In 2 patients, angiographic proof of a decrease in the size of the intracranial mass was obtained. Patients receiving glucocorticoids before or immediately after surgery usually had a benign postoperative course. Side-effects in this series consisted of gastro-intestinal bleeding in 1 patient and a moonface after a month's treatment in another. The mechanism of action of glucocorticoids in decreasing cerebral edema is not known. It may be that they restore the integrity of the cerebrovascular brain barrier. It is concluded that dexamethasone is safe and highly effective in the treatment of localized brain edema.

TWO STEP EXERCISE TEST AS A TEST OF CARDIAC FUNCTION IN CHRONIC RHEUMATIC HEART DISEASE AND IN ARTERIOSCLEROTIC HEART DISEASE WITH OLD MYOCARDIAL INFARCTION.

Hellerstein, H. K.; Prozan, G. B.; Liebow, I. M.; Doan, A. E., and Henderson, J. A. *Am. J. Cardiol.* **7:** 234 (Feb.) 1961.

The electrocardiographic responses of 92 consecutive patients with rheumatic heart disease and 100 consecutive patients with arteriosclerotic heart disease who performed a standard two-step Master exercise test were analyzed for changes in mechanism, conduction and repolarization and evaluated by five sets of criteria. The incidence of abnormal responses according to the various criteria ranged from 18 to 48 per cent. However, there was no significant difference in the incidence or types of abnormal electrocardiographic response to disease when compared with the same criteria. The incidence of abnormal responses varied according to the severity of disease as measured by the functional and therapeutic classification, regardless of the cause. The incidence of abnormal responses of patients with rheumatic heart disease was not related to age, type of valvular lesion or digitalis medication, but was directly related to the functional status of the heart as determined by the therapeutic and functional classification, cardiac chamber enlargement, presence of atrial fibrillation, and electrocardiographic response to the Valsalva maneuver. Abnormal electrocardiographic responses also occurred more commonly in patients with anterior myocardial infarction. The belief is challenged that abnormal electrocardiographic changes occurring after exercise are either diagnostic of coronary arteriosclerosis or caused solely by an insufficient blood supply to the myocardium. Reasons are presented why the inter-reaction of many facets of myocardial function should be considered in the understanding of the changes produced by exercise. The two-step exercise test is a valuable test of cardiac function but is not specific for the diagnosis of cause. The test has proved to be of value as an objective measure of circulatory fitness for brief peak exercise and has been useful for prescribing work and daily activities for patients with all types of heart disease. (From authors' summary.)

ANORECTAL SURGERY IN THE ELDERLY PATIENT.

Hodges, F. B., Jr. *South. M. J.* **54:** 268 (March) 1961.

Elderly patients may undergo proctologic surgery provided a careful preoperative investigation is made and careful postoperative care provided. However, many geriatric patients are not good surgical risks and various factors may alter the decision to operate. Malnutrition, anemia, and a lowered blood volume are likely to be found and constitute important preoperative considerations. Time taken for the correction of blood deficiencies and inadequate fluid intake is justified in view of fewer postoperative complications and a shorter convalescence. Exercise tolerance is valuable in determining any unknown cardiac condition. Patients with a history of angina, hypertension, or myocardial infarction should have an electrocardiogram and be evaluated by an internist. Operation is postponed in the case of recent myocardial infarction. Patients with cardiac decompensation and heart block should be identified in order to achieve maximal improvement before an elective operation. The pulmonary diseases found in elderly persons do not ordinarily contraindicate surgical procedures but careful evaluation is required. Diminished vital capacity places an added burden on patients undergoing operation and such conditions as emphysema, asthma, chronic bronchitis, and tuberculosis require preoperative treatment. The anesthetist must be aware of the existence of such conditions. Urinary-tract infection or obstruction must be cleared prior to proctologic surgery. Benign prostatic hypertrophy does not contraindicate surgery but preparation must be made to cope with possible complications. Elective anorectal operations may be contraindicated when there are signs of diminished renal reserve. Diabetes is not a contraindication, but pre- and postoperative management should be handled by an internist. Elderly patients with diabetes and arteriosclerosis, obese pa-

tients, and patients with a history of venous thrombosis are more susceptible to phlebothrombosis. Time spent in explaining the operation, the period of hospitalization, and the preoperative and postoperative procedures will be repaid by the confidence of the elderly patient The choice of preoperative medication and anesthesia is based upon the patient's physical condition and not his age. Sodium pentobarbital, meperidine, and atropine are given preoperatively.Unless it is contraindicated, low spinal anesthesia with tetracaine is used. Hypotension, which may occur with spinal anesthesia, is more abrupt in onset, more severe and more difficult to control in the aged. Hypertension and headache can be overcome by the sublingual administration of 0.6 mg. of nitroglycerin or the inhalation of amyl nitrate. Local infiltration is used when for some reason a low spinal or general anesthetic is not feasible. Any surgical procedure should be performed with speed consistent with good surgical principles. Postoperative care includes frequent determinations of pulse rate and blood pressure, turning the patient from side to side, encouraging deep breathing and coughing at intervals to prevent atelectasis and other pulmonary complications, and the use of sedatives, narcotics, tranquilizers, and laxatives as needed. A frequent complication in geriatric patients is fecal impaction, and it is most likely to occur in those given bulk laxatives. Early ambulation should be encouraged except in patients with some compelling reason such as a recent coronary occlusion.

ÜBER DIE BEZIEHUNGEN ZWISCHEN ALTERSULKUS UND VERKALKUNG DER ARTERIA GASTRICA SIN. IM RÖNTGENBILD (THE RELATIONS BETWEEN ULCERS OF OLD AGE AND CALCIFICATION OF THE LEFT GASTRIC ARTERY IN RADIOGRAPHS).

Holstein, J., and Stecken, A. *Fortschr. Röntgenstr.* **92:** 644, 1960; through Excerpta med. (Gerontol. & Geriatrics) **4:** 128, 1961.

The relation between arteriosclerosis of the gastric vessels and ulcers of old age has been advanced by several authors on morbid-anatomic grounds. The authors discuss 5 cases in which they could verify calcification of the left gastric artery and gastric ulcer. The clinical symptoms were characteristic for ulcers of old age. This is the first roentgenologic confirmation of the relation between these disorders.

INDICATIONS AND TECHNIQUES FOR RENOVASCULAR SURGERY ON HYPERTENSIVE PATIENTS.

Leadbetter, G. W., Jr., and Leadbetter, W. F. *J. Urol.* **85:** 105 (Feb.) 1961.

A renal cause for hypertension should be suspected in the case of onset at a young age (below 25 years), onset at an old age (about 50 years), abrupt onset or change in long-standing hypertension, or rapid progression of hypertension, or if an intravenous urogram shows a difference in renal measurement (1 to 2 cm. may be significant), an abnormal renal contour (irregularity), differences in concentration and appearance time of dye, or a gradual decrease in size or shape on one or both sides. Whenever renal hypertension is suspected, renal angiography should be performed even though an intravenous urogram shows nothing abnormal. The preoperative study also should include differential renal function studies. Despite control with drugs, surgery is indicated for hypertension caused by renal disease provided the patient is in good condition and the outlook for longevity is satisfactory. When a solitary kidney is affected, or bilateral disease is present, reparative surgery is the sole method. When the disease is unilateral, the choice lies between nephrectomy and conservative renal or renovascular surgery; the latter is preferred when feasible. For bilateral disease, two operations are preferred to a single prolonged technique, operation being performed first on the more ischemic kidney. In a patient with partial renal artery obstruction, surgery is indicated when the arterial blood pressures proximal and distal to a plaque are equal. Prerequisites to successful surgery for renal hypertension are a knowledge of problems likely to be met in anesthesia, medications, special equipment, and grafts. The technique for incision and exposure of the upper abdominal aorta and renal vessels is described.

Nephrectomy. When an atrophic kidney is associated with an obstructive vascular lesion of the opposite kidney, reparative surgery and nephrectomy are indicated. If preoperative studies do not implicate an atrophic or hypoplastic kidney, and disease is not demonstrated on the opposite side, nephrectomy probably will not alter blood pressure. However, if the contralateral kidney is normal, and the patient is a good risk, nephrectomy should be performed in an attempt to lower blood pressure. Some patients who are poor risks because of cardiovascular disease may withstand nephrectomy better than a longer operation for repair of a remediable vascular lesion. Nephrectomy is contraindicated by a solitary kidney, severe bilateral parenchymal disease, and the presence of partial or segmental atrophy and ischemia which may be removed locally. *Segmental nephrectomy* is indicated when portions of the kidney are ischemic or atrophic due to pyelonephritis or obstructive vascular lesions in minor arteries. It should be borne in mind that the ischemic zone between normal and infarcted tissue produces hypertension, and a successful operation must remove it. *Thrombo-endarterectomy* is chosen for atherosclerotic plaques obstructing the aortic-renal artery junction or the main renal artery. It is contraindicated for small renal branches and for diffuse atherosclerotic involvement of the aorta and renal vessels. The procedure is indicated when the aorta is irregular, stiff, and feels like an eggshell on palpation. It has the advantage that no homograft or artery prosthesis is introduced. *Splenorenal arterial anastomosis* is used to revascularize the kidney. It is used when endarterectomy cannot be performed on the left side because of diffuse atherosclerosis of the aorta and aortic-renal artery junction. When endarterectomy is not feasible for obstruction in the right renal artery, either splenorenal artery anastomosis or a renal artery graft may be used, the latter being preferred for diagnostic reasons, because the operation is less prolonged, and the possibility of kinking may be avoided. *Replacement of bypass grafts.* Grafting is used only when endarterectomy or splenorenal shunt is not feasible. Small-vessel homografts are not indicated for replacement of the renal artery because of a high incidence of thrombosis, recurrent atherosclerosis, and aneurysm formation. Auto-arterial grafts from the splenic or hypogastric arteries have been used successfully. Aortic homograft replacement including the renal vessels is necessary when an aortic aneurysm occurs at the level of the renal arteries. A two-stage procedure rather than this technique is advised in the case of bilateral lesions. *Resection and re-anastomosis* may be used for localized congenital narrowing of the main renal artery, arteritis, or aneurysm formation. Renal artery aneurysms should be excised, with removal of the segment of kidney supplied by the artery when the aneurysm involves a small arterial branch. *Embolectomy.* Embolism of the renal artery should be suspected in the presence of auricular fibrillation and sudden onset of acute flank pain with or without the development of hypertension. Immediate surgery is indicated when only a small branch is affected, but segmental nephrectomy should be performed if persistent hypertension develops. Embolectomy should be performed when an angiogram shows an embolus in the main renal artery.

ANTITUMOR EFFICACY OF FLUOXYMESTERONE. USE IN ADVANCED BREAST CANCER. Lowe, R.; De Lorimier, A. A., Jr.; Gordan, G. S., and Goldman, L. *Arch. Int. Med.* **107:** 241 (Feb.) 1961.

Twenty-one postmenopausal women with advanced breast cancer, who had had no previous hormonal therapy, were given 40 mg. of fluoxymesterone orally each day. Twenty-four similar patients received 100 mg. of testosterone propionate intramuscularly three times weekly. All patients were classified according to age with respect to the menopause and the predominant site of metastasis. The medications were administered by a system of random choice. Three patients (14 per cent) receiving fluoxymesterone and 7 (29 per cent) receiving testosterone propionate showed objective regression, that is, significant shrinkage of lesions and recalcification of skeletal lesions without an increase in size of any lesion or the appearance of new metastases. The regression lasted six months or longer in each

instance. These rates of regression did not differ significantly from the national figure of 20.4 per cent for testosterone propionate. With fluoxymesterone, there was little virilizing effect. Clitoral hypertrophy occurred without increased libido. Nausea occurred in 1 patient. No fluid retention or hypercalcemia was observed. Increased erythropoietic activity was noted in 5 of the 21 patients in this drug group. A marked degree of subjective improvement was lacking and several patients experienced a nervous or depressed feeling.

CANCER OF THE VULVA.

Merrill, J. A., and Ross, N. L. *Cancer* **14:** 13 (Jan.-Feb.) 1961.

Eighty-three cases of vulvar cancer, constituting 3.4 per cent of the genital cancers seen during a 22-year period, were reviewed. Sixty-eight patients were followed for three years or more. The disease occurred predominantly in postmenopausal women between 50 and 80 years of age. The most frequent presenting symptom was awareness of a vulvar lesion. Treatment delay was attributable to both the patient and the physician. Lymph node metastases occurred in 37 per cent of patients whose nodes were examined histologically. The presence of definitely enlarged lymph nodes was a poor prognostic sign, associated with lymph node metastases in over 75 per cent of cases. More than half of the metastases were present on the contralateral side, and metastases involved the deep pelvic lymph nodes (obturator, hypogastric, iliac), as well as the superficial (inguinal, femoral) nodes, occasionally without involvement of the latter. This makes bilateral removal of both deep and superficial nodes necessary if all areas of possible metastases are to be attacked. The most frequent morphologic type of vulvar cancer is a well differentiated squamous-cell carcinoma. Melanoma, Paget's disease, basal-cell carcinoma, fibrosarcoma, and adenocarcinoma of Batholin-gland origin, are rare exceptions. The absolute 5-year survival rate was 42 per cent and the corrected rate 49 per cent. The corrected 3-year survival rate was 54 per cent. Survival was related to the extent of the lesion and the mode of therapy. Patients with early lesions, treated surgically, have the most favorable prognosis. Radiation has essentially no role in the management of vulvar cancer, either as primary or palliative therapy. Since 1942, the operability rate in this clinic (University of California Hospital) has been 88 per cent, and the corrected 5-year survival rate for those treated surgically 71 per cent. A variety of surgical procedures has been performed without establishing the superiority of one over another. The fact that radical vulvectomy alone has resulted in greater survival than the "adequate" procedure of radical vulvectomy and bilateral deep and superficial groin dissection seems to indicate the value of selecting therapy on the basis of individual need. The most important factor in survival is the presence or absence of lymph node metastases, and the good results in those treated "inadequately" is probably related to the fact that lymph node metastases were infrequent in this group. The data suggest that patients with a lesion less than 3 cm. in diameter and with no palpably enlarged lymph nodes are unlikely to have metastases. However, the only patients with metastases who were cured were those treated by radical vulvectomy and deep and superficial groin dissection. Although it is apparent that the complete operation of radical vulvectomy and bilateral deep and superficial groin dissection is the one of choice if the maximal number of patients with metastases is to be cured, and that it is impossible to predict with certainty the presence or location of lymph node metastases, this procedure should be undertaken only after careful consideration of all aspects of the individual case. Radical surgery for vulvar cancer is associated with frequent complication, despite recent improvements in techniques. Lesser procedures may on occasion be successful and, in fact, the treatment of choice. Such individualization of therapy, with full appreciation of the surgical, pathologic, and oncologic principles involved, seems to represent sounder gynecologic judgment than does adherence to a rigid therapeutic dictum that may produce more discomfort than relief. (From authors' summary and conclusions.)

DIE SCHILDDRÜSE IM ALTER (THE THYROID IN OLD AGE).

Mostbeck, A. *Wien. klin. Wchnschr.* **72:** 252, 1960; through Excerpta med. (Gerontol. & Geriatrics) **4:** 117, 1961.

The iodine uptake of the thyroid was found to be decreased in advanced age. The results of tests of the hormonal phase (plasma activity, PBI^{131}, and conversion rate) in old age were at the upper limit of normal in some cases, but in about one-third of the cases they showed a shift towards hyperthyroidism, although this condition was not actually present. Determination of the plasma activity and of the PBI^{131} level after intramuscular administration of thyrotropic hormone (TSH) showed the secretion of hormone by the thyroid after TSH to be less in the elderly than in younger persons. Hormone secretion after TSH is particularly low in aged euthyroid patients who have a high PBI^{131} level. In them the reaction is even less than in hyperthyroid subjects. These findings led to the conclusion that the thyroid in old age is particularly active. The TSH reaction was shown to depend on the initial level of plasma activity: the response of patients with high plasma activity is less than that of patients with a low plasma activity. In old age, the thyroid is decreased in volume as the result of atrophy, and the peripheral hormone requirement is enhanced. Hence intense activity on the part of the aged thyroid is necessary to ensure a euthyroid state.

TECHNIC OF CONTROLLED DRUG ASSAY. II. COMPARISON OF CHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE AND A PLACEBO IN THE HYPERTENSIVE PATIENT.

Rosenbloom, S. E.; Shapera, R. P.; Goldbloom, R. S.; Pincus, J., and Shapiro, A. P. *New England J Med.* **264:** 164 (Jan. 26) 1961 .

The hypotensive effects of chlorothiazide, hydrochlorothiazide and placebo were compared in groups of 17 ambulatory patients with mild to moderately severe hypertension, by the use of a rigid statistical design. There were no significant differences among the groups with regard to age, sex, weight, duration of hypertension, levels of systolic and diastolic blood pressure, retinal changes, heart size, serum sodium level, blood urea nitrogen level, and the need for digitalis. Both chlorothiazide and hydrochlorothiazide produced a moderate lowering of systolic and diastolic blood pressure as compared with the placebo. There were no statistical differences between these two agents in hypotensive effects, but there were differences between their effects and those due to placebo. Neither were there outstanding differences among the 3 preparations in the production of side-effects. Compared with a previous study of a rauwolfia preparation, these results indicate that chlorothiazide and hydrochlorothiazide possess the advantage of slightly greater hypotensive effect, no weight gain, and few significant side-effects. This study demonstrated that with a double-blind technic combined with random sampling, a valid drug assay can be performed on a relatively small number of hypertensive subjects.

CLINICAL EVALUATION OF PHENIPRAZINE IN ANGINA PECTORIS.

Sandler, G. *Brit. M. J.* **1:** 792 (March 18) 1961.

Using a double-blind technique, a study was made with the monoamine oxidase inhibitor, pheniprazine hydrochloride (Cavodil) in 12 patients with angina pectoris. Two 3-mg. tablets were administered twice daily and the effect compared with that of a placebo. Although there was a drop in the requirement for nitroglycerin with both pheniprazine and placebo, there was no significant change in the frequency of anginal attacks following administration of the drug. Exercise-tolerance tests showed a significant increase in the amount of activity possible with pheniprazine, although the rate of performance did not alter. This apparent improvement was not reflected in the electrocardiographic findings after exertion. The increased exertion produced an increase in the severity of ischemia in 3 instances. The potential hazards of an increase in exertion without a corresponding increase in myocardial

blood supply are pointed out. Pheniprazine, the primary action of which is antidepressant, is of no value in angina pectoris and may be contraindicated.

A STUDY OF PREDNISONE THERAPY IN CHRONIC LYMPHOCYTIC LEUKEMIA.

Shaw, R. K.; Boggs, D. R.; Silberman, H. R., and Frei, E., III. *Blood* **17:** 182 (Feb.) 1961.

Prednisone was administered to 18 patients with chronic lymphocytic leukemia for a 12-week period. Antileukemic effects consisted of symptomatic improvement; regression in splenomegaly, hepatomegaly and lymphadenopathy; and a rapid increase in the total white count consisting almost entirely of an increase in lymphocytes. All of these effects were transient. The maximal changes paralleled each other: return of the white count to pretreatment levels was usually associated with recurrence of organ infiltration. With prednisone, the hemoglobin concentration rose, reticulocytosis occurred, and the platelet count tended to rise. Hematologic improvements persisted for more than eight weeks after cessation of prednisone therapy. Neutrophil levels rose initially in patients with neutropenia but returned to the pretreatment median count by the eighth week after steroid therapy. In 4 of 6 bone marrows aspirated, there was an increase in myeloid and erythroid elements. The mature lymphocyte remained the predominant cell in the marrow. In 3 patients the extent of leukemic infiltration was unchanged, in 2 moderately decreased, and in 1 increased. The changes in gamma globulin were variable and could not be related to clinical or hematologic alterations. The administration of prednisone was attended by an increase in the severity of infections. The observed increase in frequency of infections was not statistically significant. It is concluded that corticosteroids, because of the brief duration of remission induced and the increased risk of infection, should be reserved for patients with complicated hemolytic anemia and/or thrombocytopenia, and for patients with refractory disease who have bone-marrow failure.

ACUTE HYPOTENSION TREATED SUCCESSFULLY WITH HYDROCORTISONE. OBSERVATIONS IN NEUROLOGIC AND NEUROSURGICAL PATIENTS OTHER THAN THOSE WITH PITUITARY TUMOR.

Shenkin, H. A. *New England J. Med.* **264:** 645 (March 30) 1961.

In patients with cranial trauma (4 cases), brain tumor (5 cases), status epilepticus (2 cases), shock followed cerebral angiography to locate the origin of a subarachnoid hemorrhage (2 cases), and septic meningitis (1 case), an altered state of consciousness accompanied sudden failure of the circulation. Each was exposed to unusual stress and had an acute fall in blood pressure and an abrupt rise in pulse rate. Prompt reversal occurred in each instance following the intravenous administration of hydrocortisone. Similar cases of acute hypotension that would respond to this steroid probably are overlooked in neurosurgical practice because a deteriorating state of consciousness is the usual sign of a complicating cerebral edema or intracranial hemorrhage. It is not appreciated that depressed consciousness or deepening coma also can occur in patients with primary brain disease who have a failing circulation, and the falling blood pressure and tachycardia are likely to be regarded as typical manifestations of cerebral edema or compression.

CLINICAL ASSESSMENT OF ETRYNIT FOR ANGINA PECTORIS.

Sowton, E., and Oram, S. *Brit. M. J.* **1:** 794 (March 18) 1961.

In a controlled double-blind study using 0.5 mg. of glyceryl trinitrate and 10 mg. of Etrynit tablets administered sublingually, the two substances proved equally effective in relieving acute anginal pain. Etrynit is the trinitric acid ester of trimethylol propane. Thirty-five ambulant patients with angina of effort, confirmed in 33 instances by electrocardiographic changes, received two courses of each drug; 22 continued the medication and stated a preference between the drugs. With each drug 1 patient experienced palpita-

tion, nausea and headache, and one of them felt giddy. Five other patients could be freed of headaches and palpitation by dividing the dose of either drug in half. The prophylactic action of Etrynit should be studied further. Since it is equally effective, it should prove of value in patients who are unable to tolerate glyceryl trinitrate.

CLINICAL EFFECTS OF METHANDROSTENOLONE IN OSTEOPOROSIS.
Tillis, H. H. *Clin. Med.* **8:** 274 (Feb.) 1961.

Methandrostenolone (Dianabol), an anabolic agent, was given to 50 patients with osteoporosis which was of postmenopausal origin in 34 and induced by corticosteroids in 16. The patients ranged in age from 40 to 76 years and most of them also had rheumatoid arthritis. Methandrostenolone was given in an average dosage of 5 mg. twice daily for six weeks followed by a four-week rest period. Improvement observed during the first two months of therapy in 41 patients (82 per cent) consisted of relief of bone pain, increase in strength and vigor, an increased sense of well being, a feeling of mental alertness, and disappearance of fatigue and listlessness. Side-effects in the numbers of patients stated consisted of edema in 8, gastric distress in 1, hoarseness in 1, and acne in 1 patient. The edema of the ankles subsided in 4 of the patients when the dosage was reduced to 5 mg. daily. Edema in the remainder of the patients affected responded to hydrochlorothiazide. A final report will be presented after the drug has been administered for a year. The results thus far indicate that further clinical trials are warranted.

CLINICAL EVALUATION OF CANCER CHEMOTHERAPY WITH 5-FLUOROURACIL.
Vaitkevicius, V. K.; Brennan, M. J.; Beckett, V. L.; Kelly, J. E., and Talley, R. W. *Cancer* **14:** 131 (Jan.-Feb.) 1961.

5-Fluorouracil induced objective tumor regression in a variety of tumors, although commonly only at the expense of severe toxicity. Vigorous supportive therapy, combined with early treatment of complicating infections, reduced the hazards of therapy sufficiently so that in far advanced cases of otherwise untreatable breast and primary hepatocellular carcinomas, 5-FU became a clinically useful agent. In the treatment of ovarian carcinoma, the results were comparable to those with radiomimetic agents. There was no implication in carcinoma of the breast or ovary that 5-FU undergoes selective localization in the target tissue. The results can probably be explained by the nonspecific cytostatic activity of the agent against all rapidly dividing cells. Radiomimetic therapy is usually not effective in carcinoma of the large bowel. In contrast, the exceptional drug tolerance demonstrated by patients having large 5-FU-sensitive hepatomas or adenocarcinomas of the colon, and disappearance of such tolerance after development of drug resistance by the tumor, give rise to the impression that at least in these tumors there is a clinically significant drug-tissue specificity. Despite the increased tolerance of certain patients with colon carcinoma, it was always necessary to carry treatment to the point of toxicity in order to obtain an objective regression. Comparison of results in the treatment of small numbers of each of 30 additional types of solid tumor with those in the literature and with the experience of others, indicates that additional study of 5-FU should be made in the treatment of recurrent carcinoma of the cervix and in hepatocellular carcinoma. In 4 patients in the series, no improvement occurred in bladder carcinoma. These patients were previously treated with radiation at the site of recurrence and it is possible that such radiation may interfere with the response of locally or regionally recurrent carcinoma of the bladder. However, objective regression of irradiated tumors of other kinds with 5-FU has been observed. The results obtained confirmed those of previous authors that 5-FU is not of practical value in the treatment of carcinoma of the stomach. 5-FU has a narrow therapeutic range. Toxicity is regularly produced with effective doses but is manageable. The spectrum of tumors undergoing clinically valuable regressions is narrow but does include such common tumors as carcinoma of the breast, ovary and large bowel as well as hepatocellular carcinoma. (Excerpt of the authors' discussion and summary.)

ALTERN UND IMMUNITÄTSLAGE. (AGING AND IMMUNITY).

Wildführ, G. *Ztschr. ges. Hyg.* **5:** 317, 1959; through Excerpta med. (Gerontol. & Geriatrics) **4:** 122, 1961.

The relationships between morbidity, mortality, and age are demonstrated by means of a series of curves on typhoid fever, scarlet fever, poliomyelitis, hepatitis and viral influenza. Information is given on the dependence of the immunologic capacities on age. A dependence of the level of the isoagglutinin titer on age is especially distinct. A dependence of the normal heterophilic hemagglutinin or F-antibody titer on age is demonstrated. Finally, a report is given on the different behavior of the tissue reaction of young and adult animals on toxins and suspensions of bacteria. It is considered likely that following the injection of antigens, distinctive tissue reactions develop which vary with age.

NEWS AND NOTICES

SYMPOSIUM ON AGE CHANGES IN CONNECTIVE TISSUE

An informal symposium on "Age Changes in Connective Tissue and Their Clinical Implications" will be held at the New York Academy of Medicine Building on *October 31, 1961*, under the auspices of the Institute of Geriatrics of the Home and Hospital of the Daughters of Jacob. The symposium will be divided into two sessions: The morning session will deal with "Biology and Physiology of Connective Tissue" (Chairman, Dr. Nathan W. Shock, Chief, Gerontology Branch, Department of Health, Education, and Welfare). The afternoon session will deal with "Clinical Implications" (Chairman, Dr. Victor McKusick, Professor of Medicine, The Johns Hopkins University School of Medicine).

NEW PUBLICATIONS BY CENTER FOR AGING RESEARCH

Three annual publications of the Center for Aging Research, Division of General Medical Sciences, National Institutes of Health, are now available for distribution. These are: "Research Highlights in Aging, 1960," "Activities of the National Institutes of Health in the Field of Gerontology, January 1961," and "Research Programs in Aging, 1960."

"Research Highlights in Aging" presents a review of a selected number of scientific papers on research in aging carried out or supported by the National Institutes of Health. The articles reviewed range from fundamental studies in the biology of aging to studies concerned with the physical, psychological, and social problems of aging people. In addition to the scientific papers presented, the brochure includes reviews of new literature in the field, meetings of considerable importance, programs of the five major multidisciplinary centers for aging research, and training programs.

"Activities of the National Institutes of Health in the Field of Gerontology" lists all grants for aging research active on January 31, 1961. The grants are arranged in two categories—those primarily related to aging and those secondarily related to aging. In each category the grants are classified as follows: General, Major Multidisciplinary Research Projects, Structural Aspects of Aging, Physiological and Biochemical Aspects of Aging, Psychological Aspects of Aging, Social Aspects of Aging, Identifiable Disease Processes, and Training.

The third document, "Research Programs in Aging," prepared originally as background material for submission at Congressional hearings on appropriations, covers in narrative form all intramural and extramural studies supported or conducted by the National Institutes of Health in the field of gerontology.

At the conclusion of the narrative report in this document, comparative sta-

tistical summaries are given showing the number of grants and cost of these grants for a four-year period.

The final section in "Research Programs in Aging" is a bibliography listing papers presented and published during calendar year 1960 by members of the following staffs: Gerontology Branch, National Heart Institute; Section on Aging, National Institute of Mental Health; Duke University; the Albert Einstein College of Medicine; and the Center for Aging Research.

All documents are available free upon request to the Information Officer, Center for Aging Research, National Institutes of Health, Bethesda 14, Maryland.

CALL FOR PAPERS

The 19th Annual Meeting of the American Geriatrics Society will be held at the Palmer House, Chicago, Illinois, on Monday, Tuesday and Wednesday, *June 18, 19 and 20, 1962.*

Abstracts of papers for this meeting should be submitted to the Chairman of the Program Committee for consideration. Abstracts should be submitted in duplicate, double spaced, and include the title, author(s), etc. The text of the abstracts should be a complete synopsis so that the reviewer may adequately evaluate the complete work. The author should indicate at the end of the abstract whether he would present lantern slides or moving pictures (size; sound or silent). Abstracts are limited to 250 words.

Each speaker may use 20 minutes for his paper, followed by a 5-minute discussion period. Moderators will be asked to enforce the 25-minute period. Speakers are urged to check the length of their presentation.

Before January 1, 1962 send abstracts to: Program Chairman, American Geriatrics Society, 2907 Post Road, Warwick, Rhode Island.